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Annals of Surgery

39

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Surgical Science and Practice
since 1885



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Cefotan arithmetic.



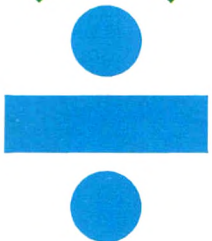
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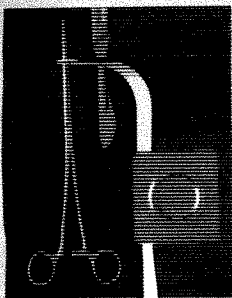
CEFOTAN[®] IM/IV
(cefotetan disodium)

In intra-abdominal and gynecologic infection
due to indicated organisms

References: 1. Nightingale CH, Smith KS, Quintiliani R, et al: The conversion of cefoxitin usage to cefotetan: An interdisciplinary approach. *Am J Surg* 1988;155(5A):101-102. 2. Sochalski A, Sullman S, Andriole VT: Cost-effectiveness study of cefotetan versus cefoxitin and cefotetan versus combination antibiotic regimens. *Am J Surg* 1988;155(5A):96-101. 3. CEFOTAN[®] (cefotetan disodium) full prescribing information issued March 1986. 4. *Physicians' Desk Reference*, ed 43. Oradell, NJ, Medical Economics Co, 1989. Mefoxin[®] (cefoxitin sodium, MSD), pp 1355-1357. 5. Carver M, Quintiliani R, Nightingale CH: Comparative pharmacokinetic study of cefotetan and cefoxitin in healthy volunteers. *Infect Surg*, April 1986 (suppl), pp 11-14. 6. Quintiliani R, Nightingale CH, Stevens RC, et al: Comparative pharmacokinetics of cefotetan and cefoxitin in patients undergoing hysterectomies and colorectal operations. *Am J Surg* 1988;155(5A):67-70.

Please see adjacent page for brief summary of prescribing information.

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CEFOTAN[®] IM/IV (cefotetan disodium)

In intra-abdominal and gynecologic infection
due to indicated organisms

For Intravenous or Intramuscular Use BRIEF SUMMARY

INDICATIONS AND USAGE

TREATMENT: CEFOTAN[®] (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:

Urinary tract infections caused by *E. coli*, *Klebsiella* species (including *K. pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris*, *Providencia rettgeri*, and *Morganella morganii*).

Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D. pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K. pneumoniae*), and *E. coli*.

Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*, *Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E. coli*.

Gynecologic infections caused by *Staphylococcus aureus** (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*, *Streptococcus* species (excluding enterococci), *E. coli*, *Proteus mirabilis*, *Neisseria gonorrhoeae*, *Bacteroides* species (excluding *B. distans*, *B. ovatus*, *B. theta* and *B. fragilis*), *Fusobacterium* species*, and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species*).

Intra-abdominal infections caused by *E. coli*, *Klebsiella* species (including *K. pneumoniae**), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B. distans*, *B. ovatus*, *B. theta* and *B. fragilis*).

Bone and joint infections caused by *Staphylococcus aureus*.*

*Efficacy for this organism in this organ system was studied in fewer than ten infections.

Specimens for bacteriological examination should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to cefotetan. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

In cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, it is possible to use CEFOTAN concomitantly with an aminoglycoside. Cefotetan combinations with aminoglycosides have been shown to be synergistic in vitro against many Enterobacteriaceae and also some other gram-negative bacteria. The dosage recommended in the labeling of both antibiotics may be given and depends on the severity of the infection and the patient's condition.

NOTE: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycosidic antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS

CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes should also be considered.

PRECAUTIONS

GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment or poor nutritional state, the elderly and patients with cancer. Prothrombin times should be monitored in patients at risk and exogenous vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

INFORMATION FOR PATIENTS: As with other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc.) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

DRUG INTERACTIONS: Although to date nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels by Jaffe reaction and produce false increases in the levels of creatinine reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approximately 8-16 times the usual adult human dose) on days 6-35 of life (thought to be

CEFOTAN[®] (cefotetan disodium)

developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approximately 2-4 times the usual human dose) only 1 of 10 treated animals was affected, and the degree of degeneration was mild.

Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

In clinical studies, the following adverse effects were considered related to CEFOTAN therapy.

Gastrointestinal symptoms occurred in 1.5% of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).

Hematologic laboratory abnormalities occurred in 1.4% of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).

Hepatic enzyme elevations occurred in 1.2% of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).

Hypersensitivity reactions were reported in 1.2% of patients and included rash (1 in 150) and itching (1 in 700).

Local effects were reported in less than 1.0% of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500). During postmarketing experience with CEFOTAN, anaphylactic reactions and transient thrombocytopenia have been reported.

DOSEAGE AND ADMINISTRATION

TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
> 30	Usual Recommended Dosage*	Every 12 hours
10-30	Usual Recommended Dosage*	Every 24 hours
< 10	Usual Recommended Dosage*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism. Alternatively, the dosing interval may remain constant at 12 hour intervals, but the dose reduced to one-half the usual recommended dose for patients with a creatinine clearance of 10-30 mL/min, and one-quarter the usual recommended dose for patients with a creatinine clearance of less than 10 mL/min. When only serum creatinine levels are available, creatinine clearance may be calculated from the following formula. The serum creatinine level should represent a steady state of renal function.

$$\text{Males: } \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

$$\text{Females: } 0.9 \times \text{value for males}$$

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED

CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. CEFOTAN is also available in a pharmacy bulk package of 10 g in 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.

1 g in 10 mL vial (NDC 0038-0376-10); 2 g in 20 mL vial (NDC 0038-0377-20); 1 g in 100 mL vial (NDC 0038-0376-11); 2 g in 100 mL vial (NDC 0038-0377-21); 10 g in 100 mL vial (NDC 0038-0375-10).

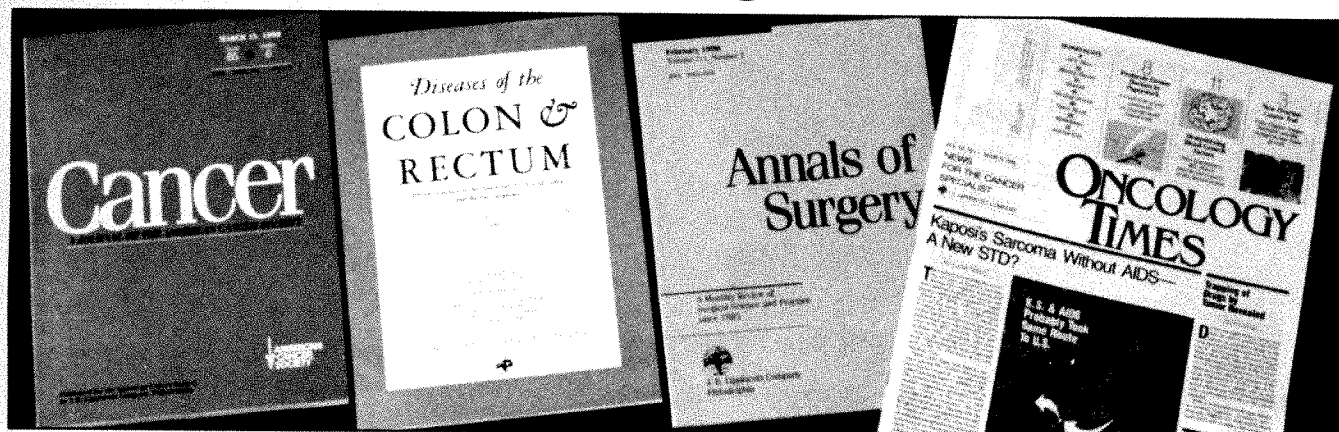
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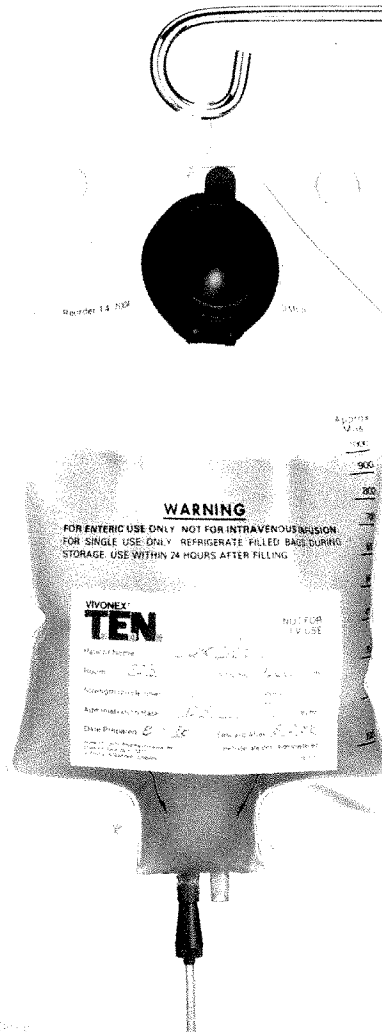
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2. Fomon HC Jr. Enteral parenteral nutrition in major abdominal surgery. *Contemp Surg* 1986;28(4-A):12-17. 3. Bower RH, Talamini MA, Goss HJ, et al. Postoperative enteral vs parenteral nutrition: A randomized controlled trial. *Arch Surg* 1986; 121:1040-1045.
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6. Philling TL, Gwyther ST, Smith RJ. Preservation of small bowel mucosa using glutamine-enriched parenteral nutrition. *Surgical Forum* 1988;37:56-57.

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C O N T E N T S

EDITORIAL

Molecules, Cancer, and the Surgeon 1

*John E. Niederhuber, M.D.
Baltimore, Maryland*

WHAT'S NEW IN GENERAL SURGERY

Molecules, Cancer, and the Surgeon: A Review of Molecular Biology and Its Implications for Surgical Oncology 3

A review of the emerging concepts of molecular tumorigenesis is presented. Normal and malignant cellular physiology is the result of interactions between specific classes of molecules. The impact of this knowledge on the future of surgical oncology is discussed.

*Jeffrey M. Arbeit, M.D.
San Francisco, California*

ORIGINAL ARTICLES

Transplantation of Two Patients with One Liver: Analysis of a Preliminary Experience with 'Split-liver' Grafting 14

Transplantation of two grafts from a single donor liver was demonstrated to be feasible in nine pairs of patients. Patient survival rate was 67%. This technique may lead to an increase in the supply of cadaver organs for liver transplantation.

*J. C. Emond, M.D., P. F. Whittington, M.D., J. R. Thistlethwaite, M.D., PH.D., D. Cherqui, M.D.,
E. A. Alonso, M.D., I. S. Woodle, M.D., P. Vogelbach, M.D., S. M. Busse-Henry, B.S., A. R. Zucker, M.D.,
and C. E. Broelsch, M.D., PH.D.
Chicago, Illinois*

Influence of Pentobarbital and Chloralose on Metabolic and Hemodynamic Changes in Liver Ischemia 23

The study suggests that hemodynamic and metabolic responses to liver ischemia and reperfusion can be influenced by anesthetics.

*Gunnel Nordström, M.D., Ola Winsö, M.D., Björn Biber, M.D., and Per-Olof Hasselgren, M.D.
Göteborg, Sweden; and Cincinnati, Ohio*

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Continued

Treatment of Highly Symptomatic Polycystic Liver Disease: Preliminary Experience with a Combined Hepatic Resection-Fenestration Procedure 30

Hepatic resection in highly symptomatic patients with massive hepatomegaly from autosomal dominant polycystic liver disease was performed with low morbidity and mortality rates. Symptoms resolved, liver function was maintained, and cystic degeneration of the remnant liver was not clinically observed.

Keith D. Newman, M.D., Vicente E. Torres, M.D., Jorge Rakela, M.D., and David M. Nagorney, M.D.
Rochester, Minnesota

Breast-conserving Therapy for Macroscopically Multiple Cancers 38

This retrospective clinicopathologic study of 586 stage I-II breast cancers treated by conservation surgery and radiotherapy suggests that macroscopically multifocal tumors are at significantly higher risk of local recurrence than are apparently unifocal lesions. Special attention to resection margins is particularly important if such patients are to be considered for breast-conserving treatment.

John M. Kurtz, M.D., Jocelyne Jacquemier, M.D., Robert Amalric, M.D., Henri Brandone, M.D., Yves Ayme, M.D., Daniel Hans, M.D., Claude Bressac, M.D., and Jean-Maurice Spitalier, M.D.
Marseille, France; and Basel, Switzerland

Inhibition of Tumor Growth and Metastasis by Chronic Intravenous Infusion of Prostaglandin E₁ 45

Chronic intravenous PGE₁ administered to tumor-bearing mice inhibited tumor growth and metastases. Inhibition of tumor growth by PGE₁ occurred in a dose-dependent manner up to 6 µg/kg/minute with no further inhibitory effect above this level. Intravenous indomethacin had no effect on tumor growth or metastases on this rodent tumor system.

Lee M. Ellis, M.D., Edward M. Copeland III, M.D., Kirby I. Bland, M.D., and Harry S. Sitren, Ph.D.
Gainesville, Florida

Management of Primary and Recurrent Soft-tissue Sarcoma of the Retroperitoneum 51

Retroperitoneal sarcomas are a difficult challenge for patient and surgeon. Complete surgical resection remains the primary effective means of treatment. Histologic grade is a significant factor in predicting outcome.

David P. Jaques, M.D., Daniel G. Coit, M.D., Steven I. Hajdu, M.D., and Murray F. Brennan, M.D.
New York, New York

Intra-abdominal Abscess After Blunt Abdominal Trauma 60

The incidence of intra-abdominal abscess (IAA) was assessed retrospectively among 4050 blunt trauma patients. Of 325 patients who underwent laparotomy, only 15 (4.6%) had IAAs, most of them in upper quadrants. Risk of abscess formation was increased by splenectomy, renal and pancreatic injuries, multiple extra-abdominal injuries, and high transfusion requirements.

Wendell A. Goins, M.D., Aurelio Rodriguez, M.D., Manjari Joshi, M.D., and David Jacobs, M.D.
Baltimore, Maryland

Preoperative Characteristics Predicting Intraoperative Hypotension and Hypertension Among Hypertensives and Diabetics Undergoing Noncardiac Surgery 66

In this prospective study of patients with hypertension and diabetes undergoing elective noncardiac surgery, patients with a low functional capacity, decreased plasma volume, or elevated mean arterial pressure were at risk for intraoperative hypotension, and those older than 70 years and with a decreased plasma volume were at risk for hypertension/hypotension. Both hemodynamic patterns correlated with increased postoperative complications.

Mary E. Charlson, M.D., C. Ronald MacKenzie, M.D., Jeffrey P. Gold, M.D., Kathy L. Ales, M.D., Marjorie Topkins, M.D., and G. Tom Shires, M.D.
New York, New York

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Suspected Myocardial Contusion: Triage and Indications for Monitoring 82

Clinical sequelae attributable to myocardial contusion were examined in 3010 patients with blunt trauma. Morbidity in those not requiring intensive care for other injuries was rare and was predicted by the admission EKG.

*David H. Wisner, M.D., William H. Reed, M.D., and Robert S. Riddick, M.D.
Davis, California*

Reduction of Intimal Hyperplasia and Enhanced Reactivity of Experimental Vein Bypass Grafts with Verapamil Treatment 87

Chronic administration of the calcium antagonist verapamil significantly reduced the development of intimal hyperplasia in autogenous vein bypass grafts in the rabbit. This beneficial effect was independent of changes in blood pressure, cholesterol level, or platelet function, and is possibly related to altered smooth muscle vasoactivity and proliferation.

*Mostafa N. El-Sanadiki, M.D., K. Simon Cross, M. Med. Sci., F.R.C.S.(Ed), John J. Murray, M.D., PH.D., Robert W. Schuman, M.D., Eileen Mikat, PH.D., Richard L. McCann, M.D., and Per-Otto Hagen, PH.D.
Durham, North Carolina*

Selective Shunt Versus Nonshunt Surgery for Management of Both Schistosomal and Nonschistosomal Variceal Bleeders 97

In 219 consecutive patients with 5 to 10 years follow-up, distal splenorenal shunt was superior in the schistosomal patients and splenectomy with gastroesophageal devascularization supported by sclerotherapy was an acceptable surgical alternative in the nonschistosomal population.

*Farouk A. Ezzat, F.R.C.S., Kareem M. Abu-Elmagd, M.D., Mohamed A. Aly, M.D., Omar M. Fathy, M.D., Nabih A. El-Ghawlby, M.D., Amgad M. El-Fiky, M.D., and Mohsen H. El-Barbary, M.D.
Mansoura, Egypt*

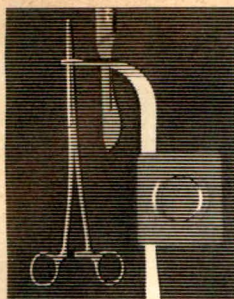
Acute Pancreatitis at Its Centenary: The Contribution of Reginald Fitz 109

Acute pancreatitis remains a disease of uncertain pathogenesis and nonspecific therapy. This review summarizes Reginald Fitz's initial characterization of acute pancreatitis, as well as more recent investigations regarding the subcellular basis of this disease.

*Steven D. Leach, M.D., Fred S. Gorelick, M.D., and Irvin M. Modlin, M.D., PH.D., F.A.C.S.
New Haven and West Haven, Connecticut*

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In intra-abdominal and gynecologic infection
due to indicated organisms

For Intravenous or Intramuscular Use BRIEF SUMMARY

INDICATIONS AND USAGE

TREATMENT: CEFOTAN[®] (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:

Urinary tract infections caused by *E. coli*, *Klebsiella* species (including *K. pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris*, *Providencia rettgeri*, and *Morganella morganii*).

Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D. pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K. pneumoniae*), and *E. coli*.

Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*, *Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E. coli*.

Gynecologic infections caused by *Staphylococcus aureus** (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*, *Streptococcus* species (excluding enterococci), *E. coli*, *Proteus mirabilis*, *Neisseria gonorrhoeae*, *Bacteroides* species (excluding *B. distans*, *B. ovatus*, *B. theta* and *B. fragilis*), *Fusobacterium* species,* and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species*).

Intra-abdominal infections caused by *E. coli*, *Klebsiella* species (including *K. pneumoniae*)*, *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B. distans*, *B. ovatus*, *B. theta* and *B. fragilis*).

Bone and joint infections caused by *Staphylococcus aureus*.*

*Efficacy for this organism in this organ system was studied in fewer than ten infections.

Specimens for bacteriological examination should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to cefotetan. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

In cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, it is possible to use CEFOTAN concomitantly with an aminoglycoside. Cefotetan combinations with aminoglycosides have been shown to be synergistic in vitro against many Enterobacteriaceae and also some other gram-negative bacteria. The dosage recommended in the labeling of both antibiotics may be given and depends on the severity of the infection and the patient's condition.

NOTE: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycosidic antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS

CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug.

Serious acute hypersensitivity reactions may require epinephrine and other emergency measures. Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes should also be considered.

PRECAUTIONS

GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment or poor nutritional state, the elderly and patients with cancer. Prothrombin times should be monitored in patients at risk and exogenous vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc.) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

DRUG INTERACTIONS: Although to date nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels by Jaffe reaction and produce false increases in the levels of creatinine reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approximately 8-16 times the usual adult human dose) on days 6-35 of life (thought to be

CEFOTAN[®] (cefotetan disodium)

developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approximately 2-4 times the usual human dose) only 1 of 10 treated animals was affected, and the degree of degeneration was mild.

Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

In clinical studies, the following adverse effects were considered related to CEFOTAN therapy.

Gastrointestinal symptoms occurred in 1.5% of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).

Hematologic laboratory abnormalities occurred in 1.4% of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).

Hepatic enzyme elevations occurred in 1.2% of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).

Hypersensitivity reactions were reported in 1.2% of patients and included rash (1 in 150) and itching (1 in 700).

Local effects were reported in less than 1.0% of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500). During postmarketing experience with CEFOTAN, anaphylactic reactions and transient thrombocytopenia have been reported.

DOSEAGE AND ADMINISTRATION

TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSEAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dosage*	Every 12 hours
10-30	Usual Recommended Dosage*	Every 24 hours
<10	Usual Recommended Dosage*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Alternatively, the dosing interval may remain constant at 12 hour intervals, but the dose reduced to one-half the usual recommended dose for patients with a creatinine clearance of 10-30 mL/min, and one-quarter the usual recommended dose for patients with a creatinine clearance of less than 10 mL/min.

When serum creatinine levels are available, creatinine clearance may be calculated from the following formula. The serum creatinine level should represent a steady state of renal function.

$$\text{Males: } \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

$$\text{Females: } 0.9 \times \text{value for males}$$

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED

CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. CEFOTAN is also available in a pharmacy bulk package of 10 g in 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.

1 g in 10 mL vial (NDC 0038-0376-10); 2 g in 20 mL vial (NDC 0038-0377-20); 1 g in 100 mL vial (NDC 0038-0376-11); 2 g in 100 mL vial (NDC 0038-0377-21); 10 g in 100 mL vial (NDC 0038-0375-10).

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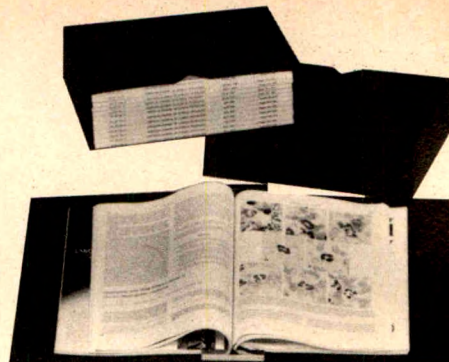
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Annals of Surgery

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EDITORIAL

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*Donald L. Morton, M.D.
Los Angeles, California*

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*Ruy G. Bevilacqua, M.D., Daniel G. Coit, M.D., Andre Rogatko, PH.D., Riad N. Younes, M.D.,
and Murray F. Brennan, M.D.
New York, New York*

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Los Angeles and Sepulveda, California*

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Rochester, Minnesota*

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*Andrew S. Klein, M.D., James V. Sitzmann, M.D., Joanne Coleman, R.N., Franklin H. Herlong, M.D., and
John L. Cameron, M.D.
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New York, New York; Montreal, Canada; Seattle, Washington; Gainesville, Florida; Cleveland, Ohio; and Fort Sam Houston, Texas

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Durham, North Carolina

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Houston, Texas

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Denver, Colorado and Bethesda, Maryland

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Los Angeles, California and San Antonio, Texas*

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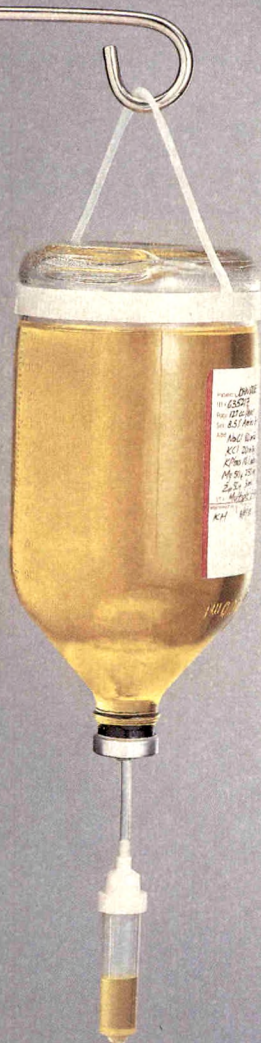
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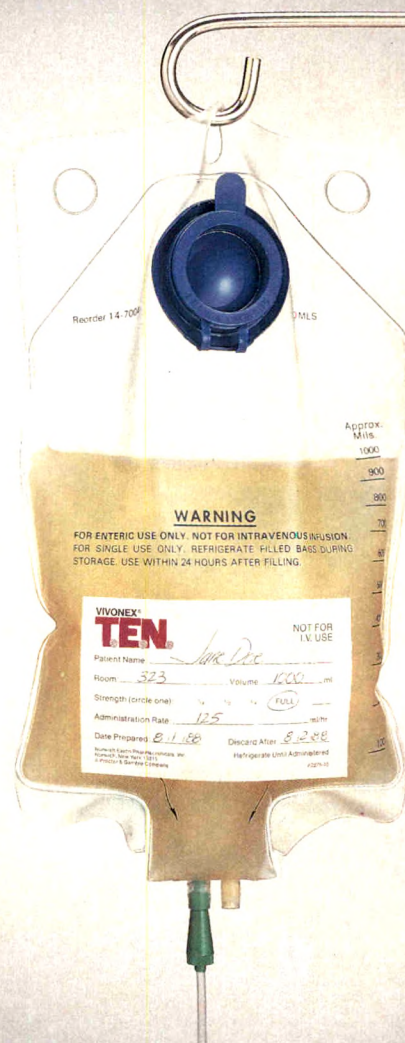
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Who Killed General Surgery? 235

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*John A. Mannick, M.D.
Boston, Massachusetts*

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*Rodney A. White, M.D., Geoffrey H. White, M.D., Mark C. Mehringer, M.D., Frances L. Chaing, M.D., and Samuel E. Wilson, M.D.
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*Henry Buchwald, M.D., PH.D., Diane K. Stoller, M.D., Christian T. Campos, M.D., John P. Matts, PH.D., and Richard L. Varco, M.D., PH.D.
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Molecules, Cancer, and the Surgeon

IN THIS ISSUE OF *Annals of Surgery*, Dr. Jeffrey Arbeit contributed an excellent overview of the molecular genetics of cancer. This review emphasizes the importance of the new era of recombinant DNA technology to the surgeon and the surgical laboratory. Recent advances using the techniques of genetic engineering have involved every field of biomedical research, including those areas of greatest interest to the surgeon. The result of these advances has been the realization that the human body is now a truly accessible genetic system for study, and recently at the first annual meeting of the Human Genome Project, leaders estimated that the DNA sequence of the entire human genome may be known within 15 years.

While Dr. Arbeit's review focuses on cancer as a disease involving genetic damage, essentially all areas of surgical investigation are driven by the desire to better understand the mechanisms of both extracellular and intracellular signal transduction in states of normal and abnormal function. Molecular biology allows us to clarify these events at the most fundamental level. As a result, academic surgery is entering a new era of laboratory investigation and, as a major clinical discipline, it is imperative that we determine if we are adequately prepared and how we can ensure that surgeons will continue to be leaders in the science of medicine.

Perhaps the most important concern to address is the role of the clinician-scientist in academic medicine. Many academicians have suggested that such an individual can no longer be competitive because of heavy clinical demands and the decreasing availability of research support. The argument is heightened by today's highly sophisticated, rapidly advancing research involving gene cloning, gene regulation, gene transfer, protein biochemistry, and the biophysics of protein structure-function analysis. These are significant arguments against the existence of clinician-scientists and, while they are directed at all clinical specialties, they are targeted especially at academic surgery.

I believe that in this era of recombinant DNA technology the clinician-scientist is more than ever essential to biomedical research. There is no substitute for experiencing daily the problems of diagnosis and the inadequacies of therapy to sharpen one's awareness of the research problems that must be addressed. The daily encounter with the patient's struggle is the greatest incentive behind discovery in medicine and is the stimulus for communication with other investigators, including our colleagues in the basic sciences. This is what drives the transfer of new discoveries from the laboratory to the patient.

Those individuals with training in both clinical medicine and basic laboratory research are vital in forming meaningful scientific collaborations between clinicians and laboratory scientists. These are the individuals who bridge the disciplinary gap. It seems clear that in this new era of molecules and genes, the clinician-scientist more than ever will be positioned to facilitate the clinical application of these discoveries and to be on the forefront of genetic therapy. While these may seem to be difficult times, with heavier clinical demands and fewer dollars for research support, academic surgery must make an even greater effort to continue to be among the leaders in research.

To reach our goals will mean significant changes in our training programs and in the structure of our academic departments. The first issue, I believe, concerns our ability to recruit the very best of medical students to careers in academic surgery. Medical students in our M.D./Ph.D. training programs are truly committed to research; and at The Johns Hopkins School of Medicine, 80% are training in molecular biology. These M.D./Ph.D. students are excited about careers in academic medicine and many, after serving clerkships in surgery, have expressed their enthusiasm for surgery as a clinical discipline. Unfortunately the discipline they embrace is rarely surgery, and what they confide is that they are not convinced that surgery will allow them to be competitive scientists as well as excellent surgeons.

To compete for students trained in molecular genetics, biochemistry, and biophysics, we need to present a surgical training program more balanced between research instruction and clinical preparation. In addition we cannot expect individuals who have already invested 7 or 8 years obtaining the M.D./Ph.D. degrees to commit to another 8 years of surgical training. We must find ways to streamline our surgical programs and the means to decrease the constraint of service requirements in structuring this training. Also it must be clear to potential trainees that our departments have the resources and the environments in which they can develop their academic careers as junior faculty members.

Thus, for those surgical trainees who want to be competitive in the future biomedical research environment, there needs to be a serious long-term commitment by both the trainee and the surgery department to ensure a period of research training comparable in length and effort to that devoted to attaining clinical skills. For those surgical trainees who possess the Ph.D. degree, a limited 2-year postdoctoral experience is appropriate and desirable, but for those surgery trainees with little previous research experience, a 2-year laboratory exposure in the middle of residency training is not sufficient to produce the desired level of competence or the needed competitiveness. In this latter group there is a subset of individuals who clearly desire the option of obtaining a Ph.D. degree but who are frustrated by training programs with little flexibility for extended absences from clinical duties.

Restructuring our surgical programs to address our future needs is not an impossible task, and the rewards for the efforts to develop a balanced training experience will pay great dividends for the individuals involved and for our academic surgery departments. It will, however, require more flexible training programs than are now common in most academic departments. Failing to make these changes will guarantee that we will not be competitive for the student-scientist or able to adequately train the novice surgeon-investigator for a competitive and credible research career. Without such individuals it is difficult to foresee academic surgeons as scientific partners who are equal to our colleagues in the other major clinical disciplines of medicine.

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Molecules, Cancer, and the Surgeon

A Review of Molecular Biology and Its Implications for Surgical Oncology

JEFFREY M. ARBEIT, M.D.

Interactions between molecules control intra- and intercellular physiology. Cancer is emerging as a disease in which individual molecules are either overproduced, mutated, expressed at inappropriate stages of development, or lost due to inheritance or aberrant mitotic division. The major players in this contest of cellular control are growth factors, growth factor receptors (GFRs), signal transducers, and dominant or suppressor/recessive oncogenes. The tumors most frequently removed by surgeons have been reported to have changes in one or another of these types of molecules. The concept of multistage carcinogenesis, whereby malignancy arises after a sequence of changes that are cumulative, and passed from progenitor to daughter cells, is also being defined as a sequence of molecular, genetic, and chromosomal alterations. Molecular antineoplastic therapy is in early stages of development at the laboratory bench. The future may see patients screened for cancer susceptibility, evaluated for adjuvant therapy, and chosen for particular treatment based on molecular analysis. The types of cancer operations and the scope of surgical resection may change as molecular techniques enhance oncologic treatment.

INCREASINGLY CANCER IS perceived by modern oncologists as a disease characterized by changes in specific molecules. These changes include alterations in the structure, regulation or quantity of growth factors and their receptors, signal transducers, and the proteins encoded by dominant or suppressor/recessive oncogenes. This review will first introduce an overview of normal cellular molecular physiology, followed by examples of changes in each of the above types of molecules in malignancy. Then the current information about the involvement of these molecular or genetic changes in cancers frequently removed by the surgical oncologist will be presented. These ideas will be brought together to formulate a molecular definition of multistage carcinogenesis, a concept that is central to understanding the formation of epithelial cancers. Finally the potential of this knowledge of molecular and genetic function to identify patients at

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risk to develop cancer or to experience recurrence after curative resection, or to facilitate the development of novel, specific, antineoplastic therapies will be discussed. This evolving understanding of the molecular physiology of cancer will ultimately change classical surgical oncology.

Organization of Molecules in the Cell

Mammalian cells are organized into tissues and organs with coordinated functions. This organization is controlled by certain classes of molecules. Growth factors are secreted by nearly all cells and act either on the cell of origin, autocrine function, nearby cells, paracrine function, or distant cells in classical endocrine fashion.¹ Each type of growth factor binds to a specific receptor anchored in the cell membrane. This binding causes the receptor to send a signal into the interior of the cell, activating molecules both in the cytoplasm and the nucleus.²

The nucleus contains deoxyribonucleic acid (DNA), which contains the genetic code for the constituents of the cell. In addition to DNA, the nucleus also contains ribonucleic acid (RNA), which has a number of functions predominantly dealing with protein synthesis, *i.e.*, ribosomal RNA, transfer RNA, and messenger RNA (mRNA). The latter molecule contains the genetic information that directly codes for specific proteins. In addition the nucleus also contains proteins that are intimately associated with DNA. These proteins replicate the DNA molecules leading to cell proliferation, repair the DNA molecules to prevent mutations, or read the genetic code, *i.e.*, transcribe DNA, to produce the RNA molecules that ultimately result in the synthesis of other proteins.³ There is a give-and-take relationship of the nuclear constituents with the cell periphery. Signals, mRNA, can emanate from

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the nucleus to produce new growth factors or novel growth factor receptors (GFRs). Growth factors or their receptors send signals to the nucleus that alter proteins associated with DNA and change either the rate of DNA synthesis or the rate of transcription of certain genes, *i.e.*, gene expression.²

The molecular changes seen in cancer cells are either exaggerations of normal physiology, or inappropriate expression of juvenile developmental patterns. Many changes seen in cancer cells have counterparts in the normal physiology of embryogenesis and organ development, lymphocyte blastogenesis, surgical wound healing, metabolic response to trauma and sepsis, and organ regeneration or hypertrophy after injury or resection.⁴ The common molecular threads in this diverse tapestry of normal physiologic functions are controlled proliferation and a regulated response to specific growth factors. In cancers proliferation and growth factor signalling are deregulated and amplified, respectively, which facilitates persistent tumor growth. The goal of modern oncology is to fully characterize the molecular mechanisms of this unrestrained malignant growth to develop specific therapies directed against the aberrant molecular physiology of the cancer cell.

Growth Factors

Growth factors are small peptides that bind to specific cell membrane receptors. This binding produces an intracellular response that results in growth and proliferation, but may also be inhibitory. The growth factors of oncologic importance⁵ are platelet-derived growth factor (PDGF), epidermal growth factor (EGF), transforming growth factors α and β (TGF α , TGF β), fibroblast growth factor (FGF), insulinlike growth factor I and II (IGF-I, IGF-II), interleukin-2 (IL-2), and colony-stimulating factors (CSF-1, CSF-2, multi-CSF). Because the last three factors are predominantly important in hematologic malignancy and immunology, they will not be further discussed in this review.

Platelet-derived Growth Factor

The principal source of PDGF is from platelets.⁶ The molecule was the first growth factor isolated and was identified by the ability of serum, in contrast to plasma, to stimulate the growth of cultured cells. When PDGF is added to nontumorigenic, long-term fibroblast lines such as NIH 3T3 cells, these cells are 'transformed,' *i.e.*, they behave like neoplastic cells, their growth rate increases, and they lose contact inhibition *in vitro*, and form tumors when injected into nude mice *in vivo*.² This cellular proliferation is the result of changes in gene expression induced by PDGF (see below). Platelet-derived growth factor exists either as a homodimer composed of two α or two

β chains or as an α/β heterodimer. Platelet-derived growth factor is produced and primarily stimulates the growth of mesenchymal cells⁶; however the growth factor is also secreted in a paracrine fashion by breast cancer cells.⁷

Epidermal Growth Factor

Epidermal growth factor is released from and acts on epithelial cells.⁵ It is an autocrine factor for cultured squamous carcinoma cells. Epidermal growth factor may also be important in the growth of colon cancer cells.⁸ Clinically EGF and the presence of the EGF receptor have been used to predict recurrences in breast cancer. The presence of the EGF receptor in human breast cancers has been correlated with a higher incidence of lymph node metastasis at initial presentation and decreased duration of disease-free survival.⁹ In node-negative patients the presence of the tumor EGF receptor can identify patients who are likely to experience recurrence, and thus possibly benefit from adjuvant chemotherapy.

Transforming Growth Factor- α

Transforming growth factor- α was originally isolated from sarcoma cell-conditioned media and was operationally defined by its ability to transform 3T3 cells.^{10,11} Transforming growth factor- α is 50% homologous to EGF and binds to the same receptor.¹¹ Transforming growth factor- α is produced by a number of different cell lines, but its most interesting physiology has been associated with breast cancer.⁷ Hormone-sensitive breast cancer cells have been found to secrete TGF- α (and also PDGF and IGF-1) as they proliferate in response to estrogen.⁷ Tamoxifen, which inhibits the growth of these cells, also blocks TGF- α secretion. Hormone-insensitive breast cancer cells can produce TGF- α without estrogen. This TGF- α secretion is also unresponsive to tamoxifen.

Transforming Growth Factor- β

Transforming growth factor- β was originally identified in the same sarcoma-conditioned media along with TGF- α , but has a completely different structure and physiology.^{11,12} Transforming growth factor- β binds to its own receptor on the cell membrane distinct from the EGF receptor. Transforming growth factor- β can cooperate with EGF or TGF- α in stimulating transformation and growth 3T3 cells. The effects of TGF- β are complex in that the molecule inhibits the growth of many types of malignant epithelial cells.¹² In contrast, other epithelial cell lines, *i.e.*, colon cancer cells produce TGF- β .¹³ Paracrine secretion of TGF- β by epithelial cells may function to inhibit the growth of normal cells in the proliferating basal layer, facilitating a selective overgrowth of neoplastic cells.

Fibroblast Growth Factor

There are several FGF-related growth factors, but the molecule exists in two predominant forms, acidic and basic. The former is found exclusively in the central nervous system, while the latter is ubiquitous and is the principal form of FGF in the body.^{8,14} Fibroblast growth factor produced by fibroblast and macrophages also is stimulatory to these cells. Fibroblast growth factor-b is strongly angiogenic and may be the principal angiogenesis factor *in vivo*, despite the recent cloning of a separate angiogenin gene.^{8,15,16} The physiology of FGF is interesting because, unlike other secreted cellular proteins, its post-translational precursor lacks a signal peptide that would normally direct the molecule to exocytotic vesicles. Fibroblast growth factor presumably enters the extracellular space by destruction of cells and lytic release. Fibroblast growth factor binds avidly to heparin and heparan sulfate, which are important extracellular matrix proteoglycans.¹⁴ Thus the extracellular matrix may be an important reservoir of FGF, and the lysis of this matrix by invasive malignant cells may result in liberation of FGF with secondary growth stimulation and angiogenesis.

Insulinlike Growth Factor-I and -II

Insulinlike growth factor-I (somatomedin-A), IGF-II (somatomedin-C), and insulin all belong to the same peptide family.¹⁷ They have a minimal amino acid sequence homology, but a similar tertiary structure.¹⁷ The similar tertiary structure enables the molecules to bind to each other's receptors, albeit at reduced affinity. Several types of malignant cells, *i.e.*, breast cancer⁷ and sarcomas,¹⁸ have been shown to overproduce IGF-I or IGF-II, which may result in enhanced autocrine growth stimulation.

Bombesin

Bombesin is predominantly found in the gut and in the brain functioning as a neurotransmitter. The molecule has been shown to transform 3T3 cells similar to PDGF.² Bombesin is produced by small cell lung carcinoma (SCLC) cells and increased numbers of bombesin receptors on these cells make up a autocrine stimulatory loop.¹⁹ The potential importance of bombesin in the proliferation of SCLC cells was demonstrated in experiments in which antibodies to the bombesin receptor were shown to inhibit the growth of cells in culture, and of tumors in nude mice.²⁰

The proliferative effects of growth factors appear to be due to alterations in gene expression consequent to their binding to their receptors. The two proteins that are markedly increased after growth factor administration are the products of the *c-fos* and *c-myc* proto-oncogenes.^{2,21,22} Within minutes after growth factor addition to the media

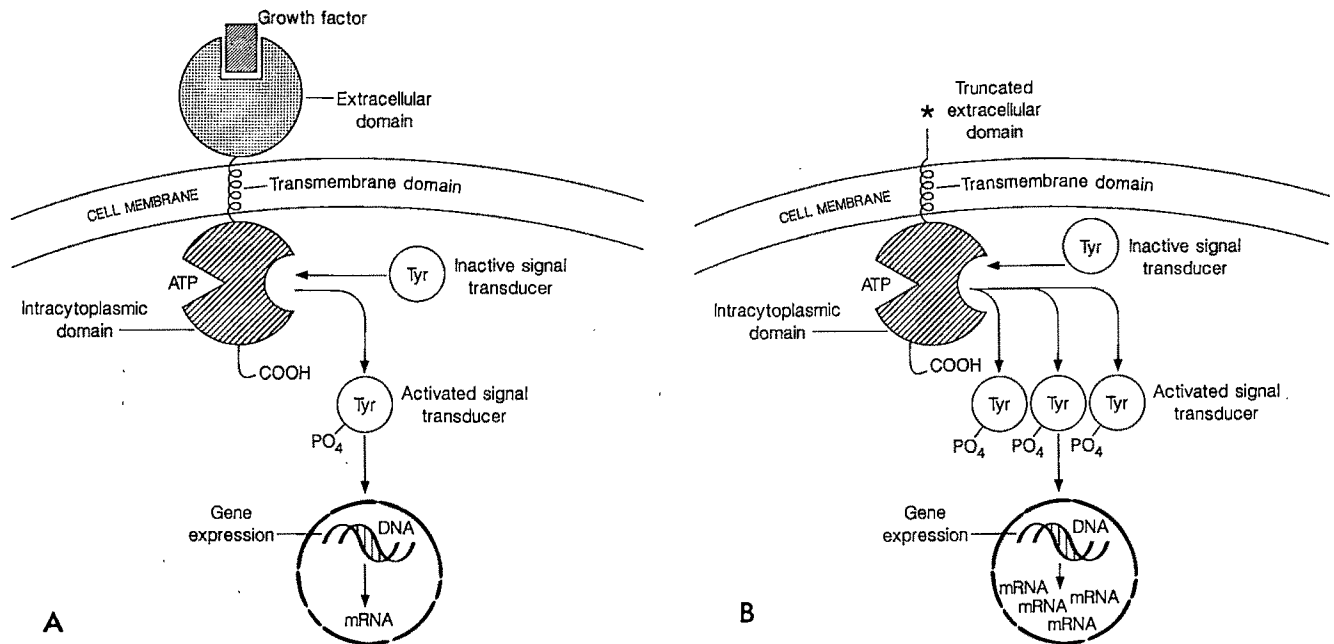
of cultured cells, there is a burst of *c-fos* expression that decreases back to baseline with 1 to 2 hours with a slower sustained rise in *c-myc* expression.²³ Both *c-fos* and *c-myc* are potent nuclear oncogenes controlling cellular proliferation.²⁴ In addition there are a number of other proteins of unknown function that are induced by growth factors.²⁵ The molecular mechanism of increased proliferation in response to growth factors will increase in complexity as the functions of these proteins and the genes encoding them are elucidated.

Growth Factor Receptors

Growth factor receptors (GFR) have both a similar structural organization and a similar intracellular physiology. They are composed of an extracellular domain, an alpha helical transmembrane segment, and an intracellular domain²⁶ (Fig. 1). Each domain has discrete functions. The extracellular domain binds ligand (growth factors, or other unknown molecules), the transmembrane helix anchors the protein and may be involved in signal modulation or transduction, and the intracellular domain binds ATP and effector proteins, resulting in protein phosphorylation on tyrosine, *i.e.*, tyrosine kinase activity.²⁶

Growth factor receptors can be grouped into three subclasses.²⁶ Subclass I includes the receptors EGF/TGF- α and the oncoproteins of *v-erb-B* and *HER-2/neu*. Subclass II is composed of the insulin and IGF receptors. Subclass III includes the PDGF and the FGF receptor and the proto-oncogenes *c-fms/CSF-1* and *c-kit*. The different subclasses are distinguished by the structure of the extracellular and intracellular domains.²⁶

When ligand binds to the GFR, the activation of the tyrosine kinase results in a cascade of proteins phosphorylated on tyrosine. Some of the proteins phosphorylated due to growth-factor activation include second messengers and nuclear DNA binding proteins.²⁷ This protein phosphorylation alters the activity of enzymes, resulting in either enhanced or decreased substrate affinity or catalytic efficiency. A key second messenger that is phosphorylated by activated GFRs is phospholipase-C (PLC),²⁸ which results in release of diacylglycerol (DAG), inosine triphosphate (ITP₃), and elevation of prostaglandins and leukotrienes. As a result of PLC activation, protein kinase-C (PKC) is stimulated, which produces the burst of *c-fos* and *c-myc* expression.²⁹ In addition activated PKC phosphorylates GFRs on threonine, which decreases their response to their growth factors, thus effectively shutting them off.³⁰ Also the GFR auto-phosphorylates itself,³¹ which also turns the GFR off because phosphorylation stimulates internalization of the receptor, *i.e.*, 'down regulation'.²⁶ Growth factor receptor signal transduction appears to require that two or more receptors bind the growth



FIGS. 1A and B. (A) A schematic illustration of a GFR, and the cellular events that follow ligand binding. The GFR has three domains, extracytoplasmic, transmembrane alpha helical, and intracytoplasmic. The extracytoplasmic domain binds the growth factor, the transmembrane helix anchors the protein in the membrane, and the intracytoplasmic domain binds ATP and is a tyrosine kinase for bound substrate proteins. The transmembrane domain was thought to transmit the signal from the bound growth factor to the intracytoplasmic tyrosine kinase, but the conformational change in the protein is probably secondary to dimerization of one receptor with another. Tyrosine phosphorylation activates certain proteins; genes that are subsequently transcribed when these proteins reach the nucleus include protooncogenes such as *c-fos* and *c-myc*. (B) Mutated GFRs may lose part of the extracellular domain, *i.e.*, the oncogene *v-erb-B*. This truncation of the extracellular domain leaves the receptor continually activated, and a constant proliferative signal is sent from the cell membrane to the nucleus.

factor as dimers or oligomers.³² This dimerization of the GFR molecules is thought to produce a conformational change in the protein that activates the intracytoplasmic tyrosine kinase. Receptor dimerization may also facilitate receptor autophosphorylation. Activated receptors also transphosphorylate other neighboring receptors, altering their affinities for their respective growth factors.³³ Receptors encoded by oncogenes frequently have truncated extracellular domains or altered transmembrane helices.²⁶ These structural changes presumably lock the receptor in a continuous 'on' mode (Fig. 1). This constitutive activation sends a continuous proliferative signal to the nucleus, which may support uncontrolled malignant cell growth.

While complex, the physiology of GFRs and neighboring membrane proteins is an example of the multiple interactions that occur when a signal is transmitted from the cell membrane to the nucleus. This complexity offers the hope that part of this molecular pathway in cancers will be amenable to therapeutic manipulation. In fact the emerging understanding of GFR physiology has led to potential novel antineoplastic therapies. Monoclonal antibodies to GFRs have been shown to decrease tumor growth.^{20,34} A new class of compounds, 'tyrphostins,' are specific, competitive inhibitors of the intracytoplasmic tyrosine kinase domain of the GFR.³⁵ These drugs can

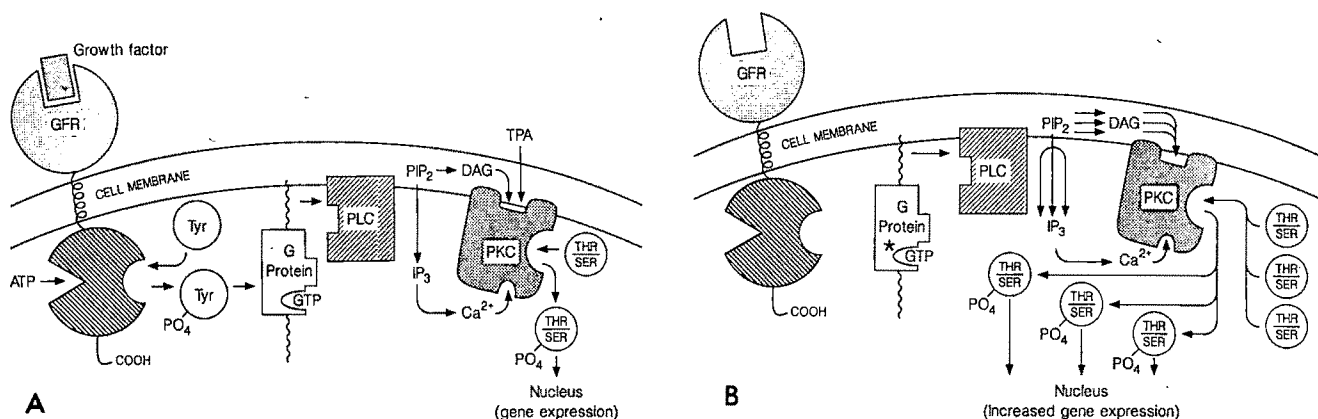
inhibit the proliferation and growth rate of malignant cells *in vitro*.³⁵

Signal Transduction

The signal transduction pathway is composed of molecules that are localized in the membranes that transmit signals from GFRs to secondary effector proteins in the cytoplasm and possibly the nucleus.²⁷ The signal transduction pathway has three components that are the phosphatidylinositol/ITP₃/DAG/Ca⁺⁺ system,²⁹ protein kinase-C,³⁶ and the GTP binding proteins, to which ras proteins belong.³⁷ Figure 2 illustrates the relationships of each of these components and shows how mutant proteins may facilitate cell proliferation.

Phosphatidylinositol System

Phosphatidylinositol is quantitatively a minor constituent of membrane phospholipids. In response to a number of stimuli, including ligand binding to GFRs, this phospholipid is split by PLC into two second messengers that have profound intracellular effects, *i.e.*, ITP₃ and DAG.²⁹ Inosine triphosphate releases Ca⁺⁺ from intracellular vesicles, which directly activates both critical metabolic enzymes and structural or mobility proteins such as actin and myosin.³⁸ Inosine triphosphate also directly stimulates



FIGS. 2A and B. (A) The multiple proteins involved in signal transduction. After a growth factor binds to its receptor a cytoplasmic G protein binds GTP and attaches to the membrane *via* a fatty acid tail. The G protein then stimulates PLC, which splits phosphoinositide-bis-phosphate (PIP₂) into ITP₃ and DAG. Diacylglycerol diffuses in the membrane and activates PKC in conjunction with calcium released from cytoplasmic vesicles by ITP₃. The tumor promoter 12-O-tetradecanoylphorbol-13-acetate directly activates PKC without calcium. Activated PKC phosphorylates proteins on threonine or serine and produces expression of proto-oncogenes such as *c-fos* and *c-myc*. (B) A G protein with a mutation at its GTP binding site, such as an activated ras oncoprotein, does not hydrolyze bound GTP and as a result is continuously activated. Phospholipase-C and subsequently PKC are continuously stimulated, without a growth factor binding to a receptor, producing a constant proliferative signal from the cell membrane to the nucleus.

a number of membrane proteins including GFRs and protein kinase-C. Inosine triphosphate is metabolized by two divergent pathways: one is rapid degradation to inosine phosphate and resynthesis to phosphatidylinositol, the other is progressive phosphorylation to molecules such as inositol tetrakisphosphate (ITP₄), ITP₅, ITP₆, and so on.²⁹ These molecules may be additional intracellular signals. Diacylglycerol also has two divergent functions. First it activates protein kinase-C, which results in a myriad of intracellular responses.³⁶ Second it is broken down to arachidonic acid and phosphatidic acid. The arachidonate is further metabolized to prostaglandins and/or leukotrienes or thromboxanes that mediate many intra- and intercellular effects.

Protein Kinase-C

Protein kinase-C is the hub of the membrane signal transduction pathway for many of the GFRs. Protein kinase-C is a cytoplasmic protein that translocates into the membrane after the release of Ca⁺⁺. It is activated by a combination of DAG, ITP₃, and Ca⁺⁺. The tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA or phorbol myristate acetate, PMA) is structurally similar to DAG and is able to directly activate PKC without ITP₃ or Ca⁺⁺.³⁶ Activated PKC phosphorylates proteins on serine and threonine, which either stimulates or inhibits their activity. Protein kinase-C transphosphorylates GFRs, which results in their down regulation. Stimulation of PKC is responsible for the increase in *c-fos* and *c-myc* expression seen after many growth factors bind to their GFRs.⁵ The intermediate steps in the transduction of the PKC stimulus to the nucleus are unknown. It appears

that GFRs stimulate PKC either by directly activating PLC, which raises membrane DAG levels, or by activating G proteins, which subsequently stimulate PLC and increase membrane DAG (Fig. 2).

G-(ras) Proteins

Proteins that bind GTP are classified as G proteins.³⁷ The bound GTP stimulates the enzyme. The stimulus decays when the GTP is converted to GDP. The system can be regulated by modulating the length of time GTP is bound before it is degraded to GDP. The paradigm for the function and mechanism of action of the G proteins is the adenylate cyclase G-protein complex that transduces the stimulus from the catecholamine receptor to adenyl cyclase.³⁷ The principle G proteins that may be involved in signal transduction after GFR stimulation belong to the ras family. The ras family are proto-oncogenes encoded by *c-Ha* (Harvey)-*ras*, *c-Ki* (Kirsten)-*ras*, or *N-ras*.³⁹ Ras proteins are globular with linear amino acid terminal and carboxy terminal tails. The current model is that after ligand binds to GFR, short-chain fatty acids bind to either the amino or carboxy terminal tails of the ras protein, GTP binds, then molecule translocates into the membrane.⁴⁰ The molecule then shuttles to PLC, or other as yet unidentified effectors, activates them, and they in turn activate PKC (Fig. 2). The signal decays as the ras protein hydrolyses its bound GTP. The ras proteins can be constitutively activated by characteristic point mutations (in codons 12, 13, or 61).³⁹ These mutations alter critical amino acids at the GTP-binding site, resulting in delayed hydrolysis, or no hydrolysis, of the bound nucleotide. These mutated proteins would send continuous proliferative

erative signals to the nucleus because of constant activation of PKC (Fig. 2). This continuous signal for proliferation may facilitate malignant transformation. Recent work has suggested that drugs that inhibit cholesterol metabolism such as compactin or lovastatin inhibit binding of the fatty acids to the tails of the ras protein, preventing their movement into the membrane and their subsequent activation of second messenger enzymes.⁴¹ Because activated ras oncogenes are found in many human cancers,⁴² these drugs may have a novel therapeutic potential. The role of activated ras oncogenes in the genesis of solid malignancies is outlined below.

Oncogenes

Oncogenes were originally identified as being the genes responsible for tumor formation by RNA tumor viruses.⁴³ Later it was discovered that these genes had been acquired (transduced) from the host genome during the process of viral excision.⁴⁴ During transduction the structure of these host genes are frequently rearranged or mutated.⁴⁴ The normal host genes are called proto-oncogenes while the mutated forms are called oncogenes. When these genes are isolated from viruses, they have a prefix 'v,' i.e., v-Ha-ras; when they are recovered from host DNA, they have a 'c' prefix, i.e., c-Ha-ras. The italics refer to the gene, whereas normal script is used to describe the protein (oncoprotein) encoded by the gene. Proto-oncogenes are involved in proliferation of cells and are expressed at defined periods in the development of organisms ranging from yeast to mammals.⁴³ Certain of these genes are reactivated during organ regeneration, wound healing, lymphocyte blastogenesis, i.e., whenever a cellular proliferative response is evoked.⁴ Oncogenes are best understood by classifying these molecules into dominant and recessive/suppressor oncogenes, and then subclassifying them according to their intracellular location, and, if known, the function of their encoded oncoproteins⁴⁵ (Table 1). The dominant genes can cause malignant transformation

by overproduction of either a normal or mutated oncoprotein. The recessive oncogenes suppress tumor formation by antagonizing the effects of dominant oncogenes.

Dominant Oncogenes

Membrane Oncogenes

This class of oncogenes encode oncoproteins that belong to one of three subclasses of GFRs outlined above. Important proteins in each of these classes include c-erb-B2 (HER-2/neu), c-kit, c-fms, and others. The former two are in the EGFR family, while the latter two belong to the PDGF family.²⁶ The prototypical example has been the v-erb-B (avian erythroblastosis) protein. This oncoprotein has an intact transmembrane and cytoplasmic domain but a truncated extracytoplasmic domain.²⁶ The truncation of the extracytoplasmic domain is presumed to result in constitutive activation of the GFR (Fig. 1).

Growth factorlike oncogenes. The only documented example of this type of oncoprotein is the product of the *sis* (simian sarcoma virus) oncogene. The *sis* product is a variant of PDGF.⁵ Normal PDGF is a heterodimer composed of α and β chains, the *sis* product is a β -chain homodimer.⁶ Constitutive production of this oncoprotein can cause malignant transformation. Receptor down regulation is ineffective in decreasing the stimulus because the PDGF receptor is activated by the *sis* oncoprotein while still inside intracytoplasmic secretory vesicles.

Signal transduction oncogenes. The ras proteins are the predominant members of this group. Their mechanism of action has been outlined above. The *src* oncogene and its phosphorylated product pp60^{src} belong to this family. Other oncogenes encoding proteins with tyrosine kinase activity and a cytoplasmic location are listed in Table 1. These oncogenes were found in human tumors, and identified by their ability to transform NIH 3T3 cells. The substrates for these proteins and their role in normal cellular signal transduction remains to be clarified. To date proteins such as PKC or PLC have not had activated oncoprotein counterparts identified, although proto-oncogenes such as *c-raf* and *c-mos* encode oncoproteins that have threonine/serine kinase activity, similar to PKC (Table 1).⁴⁶

Nuclear oncogenes. The prominent members of this group of oncogenes include *c-fos*, *c-erb-A*, *c-jun*, *c-myc*, and *c-myb*.²⁴ The group represented by *c-fos*, *c-jun*, and *c-erb-A* encode proteins that are transcription factors.⁴⁷ These oncoproteins bind to DNA and attract other proteins sequentially, eventually producing a multiprotein machine that moves along the DNA molecule and transcribes the genetic code into messenger, transfer, and ribonuclear RNA.⁴⁸ *c-jun* can potentially bind to DNA directly as a homodimer, but it preferentially binds as a heterodimer with *c-fos*.⁴⁹ The jun/fos heterodimer has an

TABLE 1. Location, Classification, and Functions of Oncogenes

Ligands	Membrane Receptors	Signal Transducers	Nuclear	
			Transcription Factors	Cell Cycle
<i>sis</i>	<i>erb-B</i> (neu)	N-ras	<i>fos</i>	<i>myc</i>
	<i>fms</i>	Ha-ras	<i>jun</i>	N-myc
	<i>kit</i>	Ki-ras	<i>erb-A</i>	L-myc
	<i>ros</i>	<i>src</i>		
	<i>trk</i>	<i>yes</i>		
	<i>ret</i>	<i>fgr</i>		
	<i>sea</i>	<i>abl</i>		
	<i>met</i>	<i>fes</i>		
		A-raf		
		B-raf		
		<i>mos</i>		

enhanced DNA-binding affinity compared to *c-jun* alone,⁴⁹ which suggests that the cell can build transcription factors from similar or disparate modular components to tailor transcription to particular conditions. The *c-erb-A* protein is the thyroid hormone receptor that binds to a particular DNA module.²⁴ The exact mechanism of malignant transformation by mutations in these transcription factors is currently unknown but presumably involves the over production of oncoproteins involved with either cell-cycle control or DNA synthesis. The mechanisms of transformation by the other nuclear oncoproteins such as *c-myc* or *c-myb* appears to be due to alterations in control of the cell cycle.²⁴ These proteins stimulate cells to progress from G1 (first interphase pause) into S (DNA synthesis phase) of the cell cycle,⁵⁰ and their overproduction prevents cells from entering a prolonged resting phase, resulting in persistent cellular proliferation.

Dominant oncogenes and surgical oncology. Dominant oncogenes are postulated to produce malignant transformation by overproduction of normal oncoproteins due to gene amplification, overproduction secondary to gene translocation, or mutational activation of oncoproteins that abrogates cellular regulation.⁴⁴ There have been many examples of solid tumors displaying one or another of these features. The oncogenes that have been frequently found in solid tumors are discussed below.

Ras oncogenes. The *ras* family of oncogenes are the most frequently activated oncogenes found in solid tumors. More than 20% of all solid malignancies contain these activated oncogenes.^{42,51} Activated *ras* genes have been correlated with lymph node metastasis in breast cancer.⁵² The most prominent role of *ras* genes has been in colon cancer where this gene is found activated in 40% to 60% of primary malignancies,⁵³ 30% to 40% of dysplastic polyps,⁵⁴ and 13% of tubulovillous adenomas.⁵⁴ The gene is usually normal in adjacent mucosa from these same patients, implying that a *ras* mutation is not an early tumorigenic event.⁵⁴

Myc oncogenes. The members of the *myc* family are *c-myc*, *N-myc*, and *L-myc*. *c-myc* expression has been found elevated in a number of solid tumors, prominently breast and lung cancers, but its most interesting role has been in Burkitt's lymphomas and leukemias.⁴⁴ In these tumors the *c-myc* gene is translocated from chromosome 8 and inserted next to the promoters for either the Ig-G or Ig-M light chains.^{44,55} This translocation of *c-myc* results in constitutive expression of the *c-myc* protein to high levels in the nucleus, which presumably stimulates proliferation of these cells. Another *myc* gene, *N-myc*, has been found to predict prognosis in patients with neuroblastoma.⁵⁶ Amplification of this gene has been frequently found in the aggressive or advanced stage neuroblastomas with short life expectancy.⁵⁶ Those patients with early stage neuroblastoma and *N-myc* amplification also have a poor

prognosis even after complete tumor resection.⁵⁷ Thus the degree of *N-myc* gene amplification may target a subset of resectable neuroblastoma patients with a poor prognosis for aggressive adjuvant therapy.

HER-2/neu. The *HER-2/neu* gene is identical to the *c-erb-B2* proto-oncogene. The gene encodes an oncoprotein that is similar to the EGFR, although the ligand for the receptor has not been identified. This gene has been found to be amplified in 25% to 30% breast and ovarian carcinomas.⁵⁸ In both tumors, this increase in gene copy number is associated with a poorer prognosis. In breast carcinomas amplification of this gene is associated with both an increased frequency of lymph node metastasis and a decreased disease-free survival.⁵⁹ The predictive value of the tumor *HER-2/neu* status is statistically significant as an independent variable distinct from lymph node status.⁵⁹

Suppressor/Recessive Oncogenes.

The existence of genes that encode proteins that suppress malignant transformation was first suggested by epidemiologic studies of a number of epithelial tumors.⁶⁰ What followed was a progressive accumulation of data from initially divergent areas of oncologic research that developed into a new scientific discipline, the study of human recessive tumorigenesis. Karyotype analysis first demonstrated that many cancers had an abnormal number of chromosomes, usually greater than the diploid 46,⁶¹ and that certain malignancies had characteristic losses of particular chromosomes, or consistent translocations of parts of one chromosome to the other, *i.e.*, the Philadelphia chromosome.⁶² Next the technique of chromosome banding was developed and each chromosome was found to possess a distinctive banding pattern.⁶³ Certain cancers that were diploid were found to have particular bands deleted, suggesting that loss of important chromosomal components could be important in tumorigenesis. Other experiments demonstrated that when normal cells were fused to their malignant counterparts, the hybrid cells lost their tumorigenic phenotype.⁶⁴ Tumorigenicity was regained when the normal chromosomes were spontaneously ejected from the hybrids, which implied that material from the normal cells could suppress malignancy. Simultaneously two other techniques appeared that markedly increased the precision of human cancer genetics and also showed that loss of specific chromosomal loci was a characteristic trait of certain malignancies. Individual chromosomes were isolated in xenographic hybrids and the genes that they contained were identified and localized, *i.e.*, mapped.⁶⁵ Concomitantly the technique of restriction-fragment-length polymorphisms (RFLPs) was developed. Restriction-fragment-length polymorphism analysis requires both a gene that is polymorphic, *i.e.*, a gene that has multiple alleles in the pop-

ulation at large so that a given individual stands a good chance of being heterozygous (a different allele from the mother and father), and close to the presumed suppressor oncogene of interest (closely linked).⁶⁶ An example of a polymorphic allele would be the HLA transplantation locus, or the minor blood group loci. The two different alleles will have a different pattern of 'restriction sites,' places where DNA digesting enzymes can cut, hence two different length fragments will be generated when human DNA is cut and analyzed with a radioactive probe specific for the polymorphic allele.⁶⁶ The genetic analysis of patients with malignancies uses peripheral blood monocytes and tumor tissue. The monocytes retain two different bands on a gel after DNA digestion and probing, while the tumor just has one band of double intensity⁶⁷ (Fig. 3). This means the tumor is hemizygous for the RFLP, and has lost heterozygosity compared to the monocytes. Because the RFLP is very near the presumed site of the suppressor oncogene, it is very likely that this locus was lost during tumorigenesis.⁶⁸ The term suppressor/recessive is derived from the ability of the cell to maintain a normal phenotype despite the loss of one parental gene. Cells are transformed into cancers when both parental copies of these genes are lost due to mutation.

Retinoblastoma. Genetic analysis of families with hereditary and sporadic retinoblastoma (Rb) have provided a paradigm for the recessive malignant transformation in humans. Patients with hereditary Rb inherit an abnormal chromosome from one of their affected parents. This inheritance is termed a germ-line mutation.⁶⁷ The condition is recessive because a normal chromosome from the unaffected parent is also present. However during the final weeks of gestation or during early infancy, another mutation occurs in a retinal cell that inactivates this remaining normal Rb gene.⁶⁷ This event is termed a sporadic somatic mutation. With the loss of both parental copies of the suppressor oncogene, malignant transformation occurs in the retinal cell (Fig. 3). In the sporadic form of this disease, both events are somatic mutations sequentially inactivating the suppressor gene locus. Restriction-fragment-length polymorphism analysis has demonstrated that the tumor tissue is hemizygous for the Rb locus while peripheral blood lymphocytes maintain heterozygosity.⁶⁷ The normal diploid chromosome number is from duplication of the remaining abnormal Rb mutant chromosome. A portion of the long arm of chromosome 13 has been found to be deleted in the tumors of these patients, which presumably is the locus for the Rb gene.^{68,69}

These patients continue to display an enhanced tissue tumorigenicity, even if cured of their Rb by surgery and radiation therapy. The incidence of second primary tumors in these patients is approximately 35% after 30 years of follow-up.⁷⁰ The second primaries are frequently osteogenic or soft-tissue sarcomas that predominantly arise

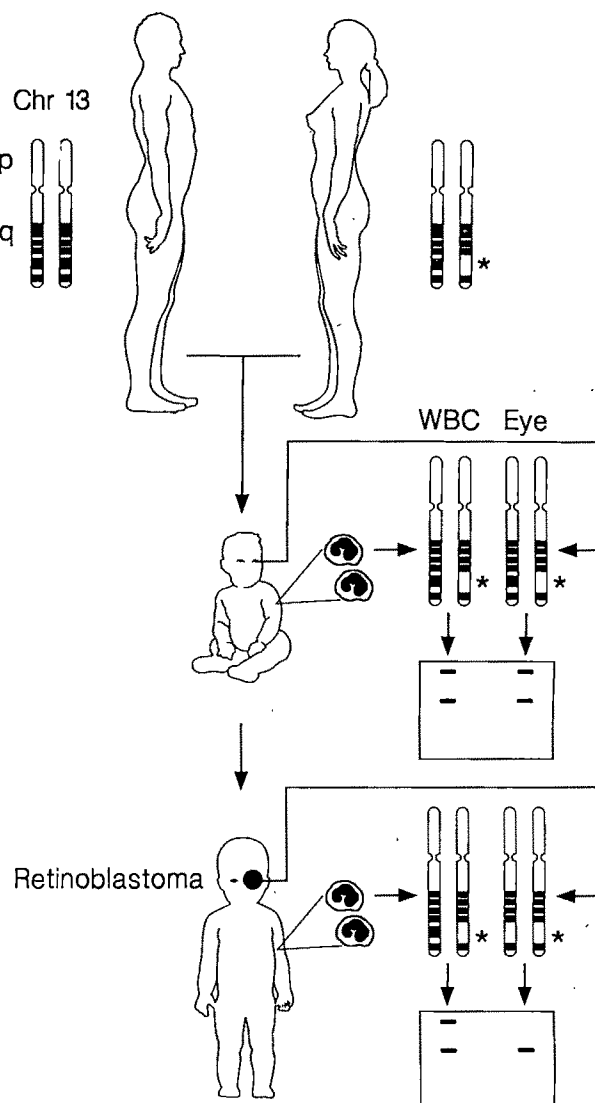


FIG. 3. The retinoblastoma (Rb) suppressor/recessive paradigm. The child inherits a chromosome 13 with a deletion in the 14th band of its long arm (13:q14). The child has a normal chromosome 13 from the father, and when monocyte DNA is digested by a restriction enzyme, two bands are seen on a gel probed with a polymorphic marker gene (restriction-fragment-length polymorphism, RFLP) close to the Rb locus. Because the chromosomal deletion is inherited, it is called a germ-line mutation. During infancy the remaining normal chromosome 13 loses its band at 14q in a retinal cell, and a tumor develops in that eye. The monocyte still has a normal chromosome, thus the monocyte retains heterozygosity while the tumor is hemizygous for the Rb gene. When both tumor and monocyte DNA are analyzed, two bands are still seen for the monocyte, while the tumor has lost one of the bands. This type of mutation is termed a sporadic somatic mutation. This genetic scheme is termed recessive because an individual with one normal and one abnormal chromosome is normal in appearance, and disease only surfaces when the normal chromosome is lost, leaving only the abnormal copy in the target tissue. Similarly the normal protein product appears to suppress the tumorigenic phenotype.

in the previous radiation port.^{70,71} When the DNA from these tumors are probed they are also found to have lost heterozygosity of the Rb locus.⁷¹ In adults the Rb gene has been demonstrated to be lost in breast and SCLCs.^{72,73}

p53 oncogene. This suppressor oncogene was originally thought to be a dominant oncogene because its overproduction could transform cells.⁷⁴ In retrospect these studies were found to be performed with a mutant version of the wild type p53 gene. Recently experiments have shown that the normal p53 gene can prevent malignant transformation of cultured cells.⁷⁵ Sequestration of the p53 gene product has been found to play an important role in DNA tumor virus carcinogenesis.⁷⁶ Clinically mutant p53 genes have been found in osteogenic sarcomas and colon cancers.^{77,78}

Wilm's Tumor

These tumors have been shown to have a deletion of the short arm of chromosome 11, which is the locus for the Wilm's tumor gene.⁷⁹ As in Rb, the peripheral blood lymphocytes of these patients are heterozygous for the Wilm's locus, while tumors are hemizygous. Minicell fusion, which introduces a normal chromosome 11 into Wilm's tumor cell lines, can reverse their tumorigenicity.⁸⁰

Lung Cancer

Both SCLC and squamous cell carcinoma of the lung have been found to consistently contain deletions of a part of the short arm of chromosome 3.⁸¹

Colon Cancer

Hereditary familial adenomatous polyposis (FAP) has been associated with deletions of chromosome 5.⁸² Deletions of the FAP locus have been found in 40% of sporadic cancers.^{54,83} In addition 40% of dysplastic polyps are also found to contain deletions of this gene.⁵⁴ The loss of this locus in polyps suggests that this is an early event in colonic tumorigenic progression. Additional chromosomal deletions have been found on chromosomes 18 and 17, but only in cancers, which suggests that these are late tumorigenic events.^{54,84} The portion of chromosome 17 that is lost in these cancers is thought to contain the p53 gene.⁷⁸

Multistep Carcinogenesis and Mechanisms of Tumorigenic Progression

The concept that cancers proceed through discrete, multiple stages before becoming fully malignant was first suggested by epidemiologic studies^{85,86} and then from work with chemical carcinogens.⁸⁷ The latter studies suggested that two stages, initiation and promotion, were sufficient to produce malignant transformation. However careful studies of the behavior of cells *in vitro* have suggested that there are multiple stages before invasive metastatic malignancy.⁸⁸ These stages include subtle acceleration of growth kinetics, subsequent activation of on-

cogenes, autocrine growth factor production, and sequential chromosome losses and duplications.

A similar scenario can be constructed for cancers *in vivo*.⁸⁹ An initial genetic change may result from an inherited susceptibility to a cancer, frequently a recessive suppressor mutation, *i.e.*, Rb or the FAP mutation, or from environmental carcinogens that activate specific oncogenes such as c-Ha-ras. Activation of a single dominant oncogene usually produces increased cellular proliferation. The increased DNA synthesis can result in an increased frequency of mistakes during replication, which may go unrepaired and become permanent mutations. If these mutations occur in additional oncogenes there is a further stimulus to continued DNA replication. During mitosis whole chromosomes or parts of chromatids may be lost or rearranged. An augmented rate of DNA synthesis may also predispose to this type of replication error. If a critical suppressor oncogene is lost, the last cellular restraint over continual cell growth may be removed, leading to malignancy. Further mutations may produce cells capable of metastasis.⁹⁰ The importance of the multistage concept is that one single oncogene or lost suppressor oncoprotein may be necessary but not sufficient to produce the complete malignant phenotype.⁸⁹

The Future

The theme of this review is that malignant transformation and the subsequent maintenance of the malignant state is orchestrated by molecules with specific functions. Cancer research is uncovering the intracellular, extracellular, and physiologic mechanisms of each of these molecules. In addition the molecular sequence of multistep carcinogenesis is being elucidated. The benefits of this research will surface as improved screening to detect high-risk individuals, more accurate assessment of the likelihood of occult residual disease, and more potent, specific antineoplastic therapies.

In the future a routine physical examination may include DNA analysis of colonic mucosa from colonoscopy specimens or from benign breast biopsies to uncover RFLP patterns, which indicate an inherited susceptibility to carcinoma in those organs. Early dietary modification or hormonal modulation could then be instituted. Resected cancers will be examined for mRNA oncogene expression patterns and RFLP analysis looking for lost suppressor oncogenes to predict those tumors that will locally or distantly recur and also those organs that will be the likely 'fertile soil' for metastasis. Systemic or local infusional drug therapy to susceptible target organs could be administered soon after resection. Even radical adjuvant therapy would be justified if the eventual site of metastasis were predictable with precision. The first beginnings of molecular antineoplastic therapy has arrived, with

agents such as the tyrosine kinase inhibitors, or lipid-lowering drugs that inhibit fatty acid attachment to ras proteins, or the use monoclonal antibodies against over-expressed growth factor receptors. With the additional data, we will be able to design more specific or combination therapies that will precisely target defined molecular pathways in the malignant cell.

Thus the continued expansion of our knowledge of how molecules work in normal tissues and in cancers will change the preoperative and postoperative care of these patients. These additional data will also change the type of operation performed on these patients. With the emergence of enhanced, potent, and specific adjuvant therapies, and the ability to accurately divine a cancer patient's future, the role of the surgical oncologist may evolve into restoration, repair, or defined specific tumor removal rather than mutilating resection.

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Transplantation of Two Patients with One Liver

Analysis of a Preliminary Experience with 'Split-liver' Grafting

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Surgical reduction of donor livers to treat small children has been performed successfully in several centers. While this procedure improves the allocation of livers, it does not increase the organ supply. We have extended reduced-size orthotopic liver transplantation (OLT) to treat 18 patients with 9 livers, accounting for 26% of our transplants during a 10-month period and have evaluated the results. In 18 split liver OLTs, patient survival was 67% and graft survival was 50%. In comparison, for 34 patients treated with full-size OLT during the same period, patient survival was 84% ($p = 0.298$) and graft survival was 76% ($p = 0.126$). Biliary complications were significantly more frequent in split grafts, occurring in 27%, as compared to 4% in full-sized grafts ($p = 0.017$). Primary nonfunction (4% versus 5.5%) and arterial thrombosis (6% versus 9%) occurred with similar frequency in split and full-size OLT ($p = \text{not significant}$). These results demonstrated that split-liver OLT is feasible and could have a substantial impact in transplant practice. We believe that biliary complications can be prevented by technical improvements and that split-liver OLT will improve transplant therapy by making more livers available.

ORTHOTOPIC LIVER TRANSPLANTATION (OLT) has evolved into a frequently used and effective treatment for patients with advanced liver disease. A major limitation to its more widespread application is availability of donor organs. While the supply of cadaver donors is adequate for adult patients, there is a critical shortage of donors for small children. As an example of the magnitude of the problem, in a recent report from the University of Pittsburgh, 25% of children accepted as candidates died while awaiting transplantation.¹ The risk is even higher for infants. Indeed we estimate that in the United States between 25% and 50% of

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infants who are transplantation candidates die before transplantation due to limitations in the organ supply.

We have analyzed the causes for the high pretransplant mortality rate in children.² This excessive mortality rate is caused by the disparity between the epidemiology of pediatric liver disease, primarily affecting infants and small children, and that of brain death and organ donation, which occurs more often in adults and school-aged children. In 1982, prior to widespread application of liver transplantation, National Health Statistics data demonstrated a bimodal mortality distribution for children with liver disease.³ The majority of children (55%) died before they reached 2 years of age. Very few deaths occur between 2 and 10 years of age, when accidents are the major cause of death. Despite the prevalence of liver disease, OLT has been performed in relatively few infants until recently. For example, only 10% of 250 patients receiving OLT in the largest pediatric experience yet reported were younger than 1 year of age.⁴ A major reason for this is the scarcity of donors in this age group.

We and others⁵⁻¹⁰ have addressed the shortage of small donors by the development of reduced-size OLT, in which cadaver livers from larger donors are reduced in size to fit into the abdominal cavity of smaller recipients. During these procedures part of the donor organ is removed along anatomic lines and discarded. In a 2-year period, while implementing a strategy in which reduced-sized OLT and standard OLT were used essentially interchangeably to treat small children, we limited the pretransplant mortality rate to 2% while achieving a post-transplant survival rate of 79% for patients receiving reduced-size grafts and 82%

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with full-sized grafts.² During this time, two thirds of the pediatric patients treated were less than 12 kg in size.

Although reduced-size OLT clearly improves the distribution of organs, it does not increase the overall supply of livers. Since July 1988 we have performed split-liver transplantation in 18 patients, 26% of transplants performed during a 10-month period. Using this technique, a second patient is treated with the portion of liver that would be discarded during preparation of a reduced-size graft. This, in effect, doubles the supply of livers available from a given donor population. In this report we analyze the results of our preliminary experience with this technique.

Patients and Methods

Study Population

This study includes all OLT performed by our surgical team between July 1988 and May 1989, during which 29 adults and 27 children were treated. Nine patients (16%) received more than one transplant. Of 68 grafts transplanted during this period, 24 (36%) were reduced-size grafts, of which 17 came from split-liver procedures. In addition the right lobe from one split-liver procedure was taken to another institution for emergency treatment of a patient in coma due to primary graft failure. Among children reduced-size and split-liver transplants accounted for 59% of grafts. Seventy-one per cent of pediatric patients were younger than 2 years, of whom 79% received reduced-size grafts. Overall we treated 56 patients with 52 donors.

Preoperative Management and Patient Selection

Medical management and selection of adult patients was according to standard clinical practice. Children were frequently assessed with regard to nutritional status, growth, and liver function by quantitative testing.¹¹ Patients were categorized into four groups depending on the level of medical support required before OLT: group 1, medically stable as outpatients; group 2, medically stable, but requiring inpatient support; group 3, medically unstable, requiring intensive care; group 4, in intensive care, requiring ventilator support. Priority was assigned according to the medical category. The weight range of acceptable donors was expanded to accommodate the performance of a reduced-size OLT under the following circumstances: (1) deterioration of stable patients to higher medical categories, (2) existence of all group 3 or 4 candidates, and (3) presence of small infants who were very unlikely to receive size-matched organs. Split grafts were performed when pairs of patients with appropriate size and urgency were present on the waiting list.

Operative Techniques

Procurement and graft preparation. Livers were procured according to standard techniques of multiple organ retrieval. All were perfused through the aorta with University of Wisconsin (UW) preservation solution.¹² Cholecystectomy was performed and the biliary tree was flushed. The livers were packed on ice in a bath of preservation solution for transportation.

The grafts were prepared in the operating room at our institution. The liver was submerged in ice cold preservation solution during the *ex vivo* dissection. The vascular and biliary structures in the hilus were dissected and lobar branches were identified. The left bile duct, hepatic artery, and portal vein were divided from the common bile duct, proper hepatic artery, and portal vein, respectively. The left and middle hepatic veins joined into a common trunk that was isolated and divided from the inferior vena cava. Orifices on the main trunks were sutured closed.

Anatomic dissection of the liver was according to the principles described by Couinaud¹³ and Bismuth,¹⁴ and as described elsewhere.⁸ The donor liver was split along the main portal scissure separating the right and the left lobes (Fig. 1) when recipients were nearly the same size. In five cases in which the patient receiving the left lobe was much smaller, the parenchymal transection was made in the plane of the falciform ligament for the creation of a left lateral lobe graft (segments 2 and 3). Segment 4 was retained with the right lobe graft in three cases to maximize the amount of parenchyma transplanted. In all cases penetrating vessels and ducts were suture ligated with fine polypropylene monofilament thread, and fibrin sealant was spread on the raw surface of both grafts. The right lobe graft consisted of segments 1 and 5 to 8, with segment 4 in three cases. All common structures (*i.e.*, portal vein, celiac trunk, common bile duct, and inferior vena cava) remained attached to the right lobe grafts. The left graft consisted of segments 2 to 4 in 4 patients, and segment 2 and 3 in 5 patients. The left lobar branches constituted the vascular and biliary structures for these grafts. To increase the length of the vessels for anastomosis, interposition grafts consisting of the external iliac artery in continuity with the common iliac artery and the terminal inferior vena cava or iliac vein from the donor were sewn to the left hepatic arterial and portal venous branches, respectively (Fig. 2). The preparation of the two grafts required 3 to 4 hours.

Recipient Operations

Recipient hepatectomy in the first patient was performed during preparation of the first graft, which was then implanted immediately, while the second graft was being prepared. The second recipient hepatectomy was performed during preparation of the second graft. Graft

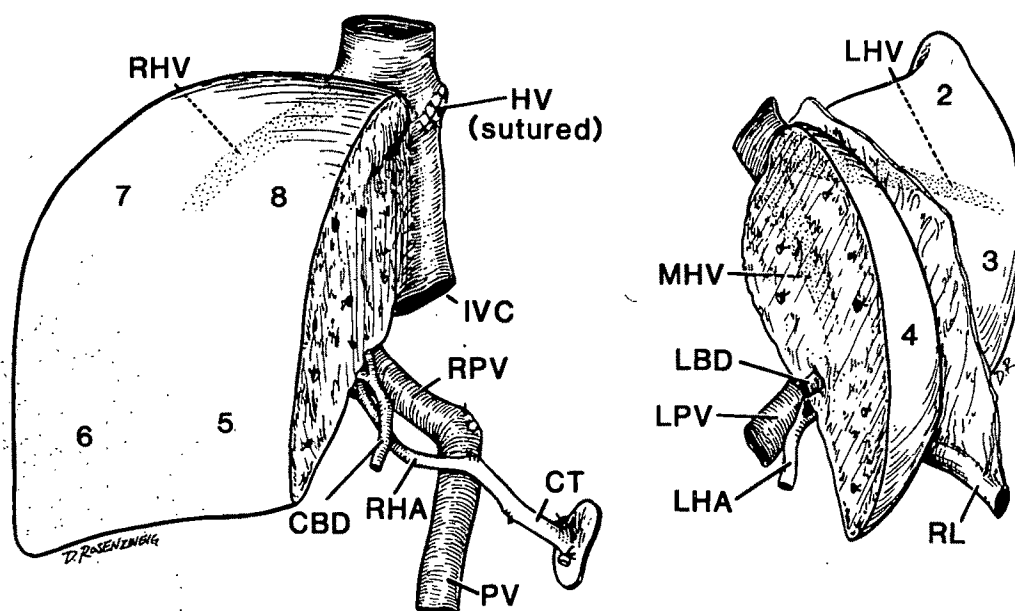


FIG. 1. Diagram of the two grafts after preparation from one donor liver. Note that all the main vascular and biliary structures remain attached to the right lobe and that the left lobe is supplied by lobar pedicles. IVC, inferior vena cava; PV, portal vein; CT, celiac trunk; CBD, common bile duct; HV, hepatic vein; RPV, right portal branch; RHA, right branch of hepatic artery; RHV, right hepatic vein; LHA, left branch of the hepatic artery; LPV, left portal branch; LBD, left bile duct; LHV, left hepatic vein; MHV, middle hepatic vein. Numbers indicate hepatic segments according to Couinaud⁹.

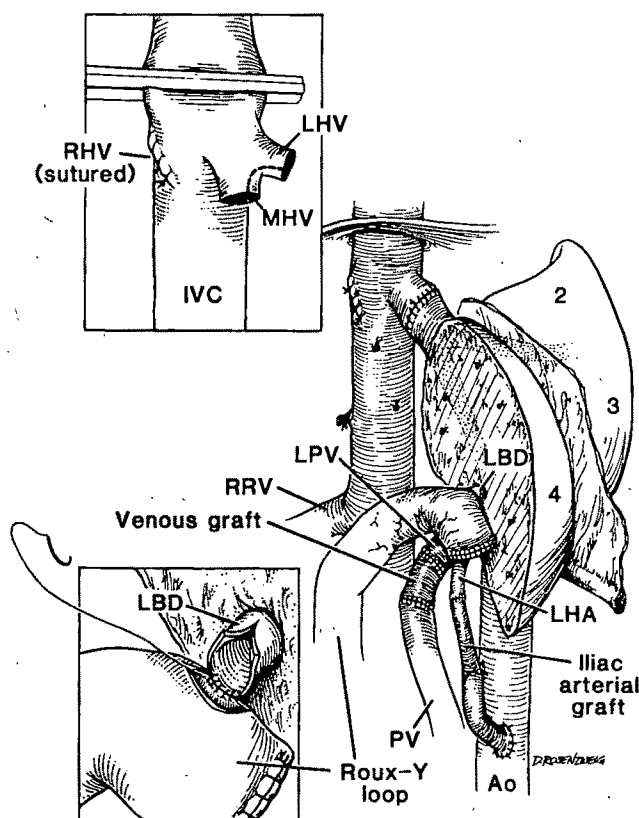


FIG. 2. The left lobe graft after revascularization, as in patients A2 and B2. Note the preservation of the inferior vena cava and the anastomoses of the segmental pedicles using interposition grafts. Upper square shows the preparation of the inferior vena cava and hepatic veins using the common trunk of the left and middle hepatic veins for suprahepatic venous anastomosis. Lower square shows the anastomosis of the Roux-Y loop on the left hepatic duct, which is enlarged by an anterior spatulation.

ischemia ranged from 7.5 to 21 hours. Recipient operative times ranged from 5.5 to 12 hours.

In patients receiving the right lobe graft, the native liver, including the retrohepatic vena cava, was mobilized and removed. The graft was implanted orthotopically by suturing the inferior vena cava above and below the graft, the portal vein, and the hepatic artery. All anastomoses were similar to standard OLT and interposition grafts were not required. Biliary reconstruction was done with a Roux-en-Y cholangiojejunostomy or to a single right hepatic duct in eight cases and incorporating a secondary segmental bile duct in one other.

Implantation techniques varied in several respects for patients receiving left lobe grafts and are summarized in Table 1. The hilus of the recipient's liver was dissected with division of the hepatic artery and common bile duct. The liver and the inferior vena cava were then mobilized from the retroperitoneum, and vascular exclusion of the liver was achieved by clamping the vena cava above and below the liver and division of the portal vein. The liver was then removed with preservation of the inferior vena cava in seven of nine cases. In these cases the caval orifice of right hepatic vein and several smaller accessory hepatic veins were sutured closed and the common trunk of the middle and left hepatic veins was used for the hepatic vein anastomosis (Fig. 2). Patient 2L had organized thrombosis with complete obliteration of the subhepatic cava. The left hepatic vein of the graft was anastomosed directly to the remaining suprahepatic cava. In patient 9L, excision of the vena cava with the liver was performed as in standard OLT, with creation of a vena cava replacement from the middle hepatic vein of the graft, as de-

TABLE 1. Split-liver OLT: Technical Details of Left Lobe Grafts

Patient	Graft*	Artery†	Portal Vein‡	Hepatic Vein§
1L	2-4	I, A	I	LHV
2L	2-4	I, HA	I	VC
3L	2, 3	IH	E	LHV
4L	2-4	IH	I	LHV
5L	2, 3	IH	I	LHV
6L	2, 3	IH	I	LHV
7L	2-4	IH	I	LHV
8L	2, 3	IH	E	LHV
9L	2, 3	IH	E	VC

* Hepatic segments implanted (Couinaud).

† Arterial anastomosis: IA—iliac artery interposition graft to recipient aorta.

IH—iliac interposition graft to recipient common hepatic artery.

‡ Portal vein anastomosis: I—iliac vein interposition graft.

E—direct anastomosis without graft.

§ Hepatic vein anastomosis: LHV—left hepatic vein end-to-end.

VC—Replacement of vena cava with middle hepatic vein.

scribed by Ringe et al.¹⁵ The portal vein was sewn end-to-end to an interposition graft in six cases, while direct anastomosis was possible in three. In recipient 1L, the interposed iliac artery was passed through a retropancreatic tunnel and anastomosed to the infrarenal aorta, while in the remaining cases, the interposed iliac artery was anastomosed to the common hepatic artery. The left bile ducts measured 1 to 5 mm and were enlarged by anterior incision (Fig. 2), and Roux-en-Y cholangiojejunostomy was performed in all cases. Inclusion of more than one ductal orifice in the biliary enterostomy was required in four of nine cases.

Data Analysis

Proportions were compared using 2×2 contingency tables and calculating χ^2 with Yates correction for continuity.

Results

Recipients and Operative Data

Preoperative data on 18 patients receiving split transplants is summarized in Tables 2 and 3. Pretransplant diagnoses were similar to our overall transplant experience,¹⁰ with a predominance of biliary atresia in children. The oldest child treated was 32 months and all children weighed 12 kg or less. Overall 7 of 18 recipients of split-liver grafts were critically ill before the transplant, with 5 patients requiring ventilator support. Six were stable at home. Table 4 presents sizes and blood types of donors and recipients size and the grafts used. Donors ranged in weight from 16 to 75 kg.

TABLE 2. Preoperative Data from 13 Children Receiving Split-liver Transplants

Patient	Age	Weight	Indication for Transplantation	Status*
1R	7 mo.	4.8 kg	Alpha-1-antitrypsin deficiency	1
1L	3 mo.	2.1 kg	Subacute liver failure	4
2R	16 mo.	9.3 kg	Biliary atresia	1
2L	5 mo.	4.1 kg	Biliary cirrhosis	3
3L	9 mo.	5.1 kg	Biliary atresia	2
4R	8 mo.	6.4 kg	Biliary atresia	1
4L	4 mo.	4.9 kg	Neonatal hepatitis	1
5L	11 mo.	9 kg	Biliary atresia	2
6L	14 mo.	11 kg	Biliary cirrhosis	1
7R	25 mo.	9 kg	Biliary cirrhosis	3
7L	11 mo.	6 kg	Biliary atresia	2
8L	32 mo.	8.2 kg	Biliary cirrhosis	2
9L	24 mo.	12 kg	Primary graft nonfunction	4

* Status: 1 = at home; 2 = in hospital; 3 = ICU bound; 4 = ICU bound, on ventilator.

Deaths and Complications (Table 5)

Early deaths (within 7 days of OLT). Three patients died within 96 hours of transplantation. Patient 1L was a 2.1-kg infant with tetralogy of Fallot and idiopathic cirrhosis who developed congestive heart failure and died 48 hours after OLT. Biochemical indices of graft function and histology were satisfactory. Patient 7L developed infarction of the entire midgut and liver. The graft was ABO incompatible and neither arterial nor venous thrombosis was identified at laparotomy or subsequent pathologic examination. Patient 9R was at another institution and was 5 days after having received a primary OLT. He was *in extremis* due to graft nonfunction. After preparation of the left lateral lobe graft for patient 9L in our institution, the right lobe was flown to the second institution and implanted after 18 hours of cold ischemia. The patient was unstable during the procedure and suffered cardiac arrest after reperfusion, which was apparently due to metabolic causes.

Late Deaths

Three other patients died between 25 and 45 days after transplantation. Patient 5R was a 20-year-old man with

TABLE 3. Preoperative Data of Five Adults Receiving Split-liver Transplants

Patient	Age	Weight	Indication for Transplantation	Status*
3R	20 yrs.	50 kg	Cirrhosis	1
5R	20 yrs.	60 kg	FHF	4
6R	57 yrs.	68 kg	Chronic rejection; graft infection	2
8R	36 yrs.	51 kg	Cirrhosis	4
9R	49 yrs.	65 kg	Nonfunction	4

* Status: 1 = at home; 2 = in hospital; 3 = ICU bound; 4 = ICU bound, on ventilator.

TABLE 4. Split-liver OLT: Operative Data for Donor and Recipients

Donor		Recipient (R) Lobe					Recipient (L) Lobe				
Wt (kg)	Blood Type	Pt	Wt	Blood Type	Graft*	Time†	Pt	Wt (kg)	Blood Type	Graft	Time
16	O	1	4.8	B	5-8	15	1	2.1	A	2-4	18
16	B	2	9.3	B	5-8	14	2	4.1	O	2-4	13
31	O	3	50	AB	4-8	17	3	5.1	B	2, 3	20
17	O	4	6.4	O	5-8	10	4	4.9	O	2-4	7.5
47	B	5	60	O	4-8	11	5	9	B	2, 3	10
64	O	6	68	O	4-8	19	6	11	O	2, 3	21
32	A	7	9	A	5-8	12	7	6	O	2-4	12.5
61	O	8	51	O	5-8	12	8	8.2	A	2, 3	13
75	O	9	65	B	5-8	18	9	12	O	2, 3	12

* Hepatic segments according to Couinaud.

† Total ischemic time (hours).

fulminant hepatic failure. He was transplanted while in stage IV coma. An ABO-incompatible right lobe graft was used, which included segment 4. After operation the patient awoke, recovered nearly normal liver function, and was discharged from the intensive care unit. Fourteen days after the procedure, he developed biochemical and histologic evidence of rejection. This was steroid unresponsive and was treated with 12 days of OKT3 (Ortho Pharmaceuticals, Raritan, NJ). The patient developed a biliary leak and was returned to the operating room where arterial thrombosis was identified. In addition to bile duct necrosis, segment 4 was also infarcted. Retransplantation was performed, but the patient died of septic complications 30 days later.

Patient 6R was 57 years old with chronic rejection and an intrahepatic abscess 5 months after primary OLT for the treatment of sclerosing cholangitis. He was treated with an ABO-compatible right lobe graft that included segment 4. Seven days after operation the patient developed massive hemorrhage due to disruption of the arterial anastomosis and complicated by necrosis of segment 4. The patient developed septic complications and died 25 days later after a third OLT.

Patient 7R was a cachectic 25-month-old child with biliary cirrhosis. At the time of transplantation, the patient was in the intensive care unit because of recurrent variceal hemorrhage. The patient received an ABO-compatible

right lobe graft. After initial good graft function, the patient developed severe rejection, which was refractory to therapy, and died 25 days later of septic complications shortly after a second OLT.

Graft Failure Successfully Treated with Retransplantation

Patient 4L was treated with a left lobe graft but developed intractable ascites after transplantation. Ultrasound examination and biopsy demonstrated extensive fibrosis of the graft, although the hepatic artery, portal vein, and hepatic veins were patent. At the time of retransplantation, partial obstruction of the hepatic vein anastomosis was identified. The patient is alive with normal liver function 5 months after retransplantation.

Patient 5L received a left lateral lobe graft prepared from a donor in which segment 4 was preserved with the right lobe. The patient had three separate biliary radicals anastomosed to the primary Roux-en-Y. Biliary necrosis occurred and attempted repair of the biliary fistula lead to obstruction. The graft was replaced with good results.

Patient 6L received an ABO-compatible left lobe graft with a cold ischemic time of 21 hours. The graft failed to function and was replaced within 24 hours, and the patient was discharged 10 days later without further difficulties.

Overall Graft and Patient Outcome

Split grafts. Graft and patient outcome for 18 split liver grafts is summarized in Table 6. Nine of 18 patients are alive with good function of the primary split graft after a postoperative follow-up from 2 to 12 months. Three additional patients are alive with a second graft. Overall 12 of 18 (67%) patients are alive after split-liver grafting. Graft survival for these split liver grafts is 50%.

Comparison of Results of Split and Full-size OLT

In 36 patients who received full-size grafts during this period, 84% of the patients are alive between 1 and 10

TABLE 5. Surgical Complications in 18 Split-liver Graft Transplants

Complication	Incidence	Patient
Hemoperitoneum	6/18 (33%)	1L, 4L, 5L, 6R, 7L, 8R
Biliary leakage	5/18 (27%)	3L, 5R, 5L, 6R, 8R
Partial necrosis	2/18 (11%)	5R, 6R
Graft nonfunction	1/18 (6%)	6L
Arterial thrombosis	1/18 (6%)	8R
Portal vein thrombosis	1/18 (6%)	5L
Intraoperative cardiac arrest	1/18 (6%)	9R
Mesenteric infarction	1/18 (6%)	7L
Postoperative cardiac failure	1/18 (6%)	1L

TABLE 6. *Graft and Patient Outcome for 18 Split-liver Transplants*

Status*	Incidence	Patients	Follow-up (months)
Alive with primary graft	9/18 (50%)	1R, 2R, 2L, 3R, 3L, 4R, 8R, 8L, 9L	2-12
Alive with retransplant	3/18 (17%)	4L, 5L, 6L	6-8
Died	6/18 (33%)	1L, 5R, 6R, 7R, 7L, 9R	
Total actual patient survival	67%		
Total graft survival	50%		

* Status as of July 1, 1989.

months, with a primary graft survival of 76%. These results were better than those achieved with split-liver procedures, but the differences were not statistically significant ($p = 0.298$ for patient survival and 0.126 for graft survival). Patients receiving a full-size graft were predominantly adults and older children. The level of preoperative medical support was slightly less severe for patients receiving full-size grafts. Forty-seven per cent of patients receiving a full-size graft were waiting at home at the time of transplantation, in contrast to 33% for patients receiving split grafts. Twenty-eight per cent of patients receiving full-size grafts were in intensive care as compared to 38% of patients receiving split grafts.

Blood group incompatibility resulted in poor survival in both groups: only one of five patients receiving ABO-incompatible grafts survived. The one survivor was patient 2L, who received a split left lobe graft. The other four, two receiving split-grafts and two receiving full-size grafts, died.

In general complications were more frequent in patients receiving split-liver OLT. Hemoperitoneum occurred in 33% of split grafts and in 14% of full-size grafts ($p = 0.086$). Biliary leakage complicated 27% of split OLT and 4% of full-size OLT ($p = 0.017$). In contrast to these clear differences, arterial thrombosis (6% *versus* 9%) and primary graft nonfunction (6% *versus* 4%) occurred with similar frequency in the two groups. No trends could be identified in the occurrence of extrahepatic complications.

In the small group of 7 reduced-size OLT performed during this period, graft survival was 100%. Hemoperitoneum occurred in one case (14%). There were no biliary leaks, vascular complications, or nonfunctioning grafts in this group. Complications due to the parenchymal transection, including partial graft necrosis, or leakage of blood or bile from the cut surface did not occur.

Function of Split-liver Grafts

Biochemical parameters of graft function are presented in Table 7. The functional parameters, in particular the serum bilirubin and prothrombin times, are within the

normal range for all patients. Representative ^{99}Tc -HIDA excretion scans are shown in Figure 3 to demonstrate the anatomic positioning of right and left lobe grafts.

Discussion

The results of the present series demonstrate that split-liver transplantation can be used successfully to treat two patients with one donor. In this preliminary experience, patient survival was 67% and graft survival was 50%. While the outcome was not as good as in our patients receiving full-size OLT during this period (who experienced 84% survival and 76% graft survival), the results clearly demonstrate the feasibility of the procedure.

The circumstances that prompted us to perform the first split-graft liver transplants in infants illustrate how this procedure can alter the practice of liver transplantation. Patient 1L was the smallest patient ever to receive a liver transplant. He was in an intensive care unit, dying of liver disease. No whole organ, not even a newborn's liver, could have served his needs because of his size. Thus he required a reduced-size transplant. However it seemed that the extreme complexity of the case would limit the chances for successful transplant, which made it difficult to justify using a pediatric donor just to provide a reduced-size graft. By splitting the liver, the impact of transplanting this child, who had a marginal chance for success on the pediatric donor pool, was lessened. Patient 2L, who was also very small and had other congenital anomalies, is another example of such reasoning with a better outcome. Patients 1R and 2R were relatively stable at the time of operation but were small and had rapidly progressing liver disease. As long as they remained at home, and therefore at relatively low priority, the United Network for Organ Sharing (UNOS) would have been unlikely to provide them with appropriate-sized grafts. Obviously they could be best served by transplantation before the onset of severe complications and the need for hospitalization. Thus the split-liver procedure also improved their care by allowing

TABLE 7. *Function of Split-liver Transplants*

Name	Follow-up	Total Bilirubin (mg/dL)	ALT (IU/L)	Alk. Phos. (IU/L)	Prothrombin Time (seconds)
1R	12 mo.	0.4	20	217	12.6
2L	9 mo.	0.5	26	221	12.4
3L	7 mo.	1.5	176	458	12.0
8L	5 mo.	0.8	29	464	12.0
9L	6 wks.	0.8	19	421	15.2
4R	6 mo.	0.3	53	259	12.6
2R	9 mo.	0.3	189	3529*	12.5
3R	6 mo.	0.8	18	24	12.6
8R	5 mo.	1.1	24	62	11.5

* All 'bone' isoenzyme in rapidly growing infant.

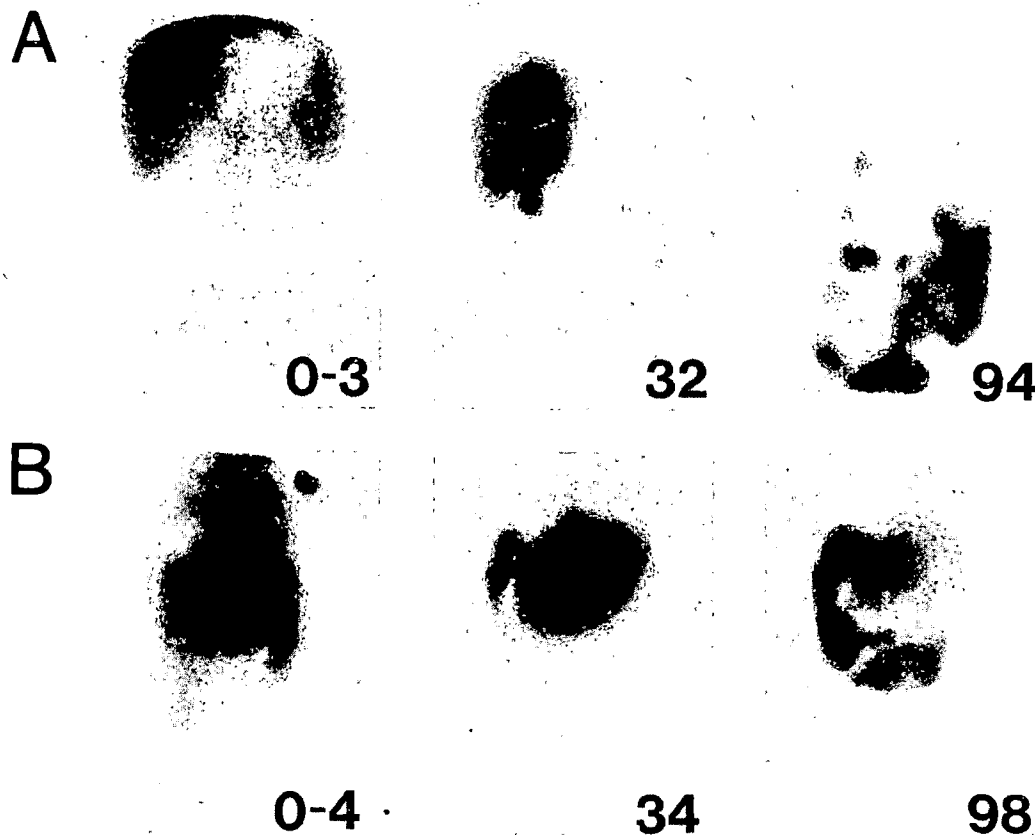


FIG. 3. Representative ^{99}Tc -HIDA excretion scans are shown for two patients. (A) demonstrates normal function of a right lobe graft in patient 3R, a 20-year-old woman 5 months after OLT. Postinjection times 0-3, 32, and 94 minutes are shown. (B) Slightly delayed parenchymal excretion in patient 9L, a 24-month-old boy during a rejection episode one month after OLT. Postinjection times 0-4, 34, and 98 minutes are shown.

them to be transplanted at the priority level of the left-lobe recipients.

While the use of reduced-size and split-liver transplants is justified in small children, their role in adult transplantation is at issue. The principal difference at this time is the relative abundance of donors for the two groups. In our previous analysis of donor use in Illinois in 1987, we found that livers were used in 100% of visceral organ donors less than 4 years of age, whereas less than 50% of adult donors supplied livers.² The use of livers is increasing steadily; however while in 1987 livers were procured from 36% of organ donors, this figure has increased to 52% in 1988, and 71% in 1989 (Regional Organ Bank of Illinois, personal communication). Within the coming years, adults will probably face the same shortage of donors presently experienced in children.

In our initial efforts to treat adults with split transplants, we selected patients in relatively stable medical condition, which is probably not appropriate at this time. However our selection of an elective patient was based on our confidence with earlier results of reduced liver grafting and the relative safety demonstrated for recipients of right lobe grafts.² Our last three adult experiences have been in critically ill patients who required ventilator support in whom there was an urgent need for a graft and in which exceptional measures were justified. The last case represents a

unique experience in which two patients in coma due to primary graft failure, a child in our institution and an adult in another institution, were treated with left and right lobe grafts from a single donor. At the time of donor procurement there were 20 patients in the most critical status for liver transplantation in the UNOS computer registry.

Analysis of the failures in our experience indicates several problems that can be overcome by modification of the technique. The quadrate lobe (segment 4) must be handled properly for the procedure to be successful. Although based on external morphology, it seems to be part of the right lobe of the liver; because it lies to the right of the falciform ligament,¹⁴ segment 4 is functionally part of the left lobe of the liver.¹³ Its blood supply and biliary drainage originate at the trifurcation of the left portal vein at the base of the round ligament. Efforts to preserve segment 4 with the right lobe can cause dangerous complications for both grafts. For the right lobe graft, the blood supply and the hepatic venous drainage for this segment can be compromised, with resulting necrosis. Two adults who received a right lobe graft, which included segment 4, died of sepsis complicating tissue necrosis. Leaving segment 4 with the right lobe can also compromise the left lobe graft because preservation of the biliovascular pedicle of segment 4 involves dissection of the biliary confluence

of segments 2 and 3. In two of the children receiving left lobe grafts in which the segment 4 remained with the right lobe, biliary dehiscence occurred.

These complications, that is necrosis of the segment 4 in the right lobe grafts and compromise of the biliary radicals for the left lateral lobe graft, can be avoided in the following manner. First, if the split-liver graft is being performed for the treatment of two infants of relatively equal size, a complete right lobe and a complete left lobe provide optimal positioning and parenchymal mass for both patients. The dissection of the hilar elements for the left lobe should be extremely limited and extend just to the left of the primary bifurcation of the portal vein and the confluence of the right and left hepatic ducts. Proximal dissection of the bile duct to the level of the round ligament, where the left duct structures trifurcate, is dangerous and unnecessary. The right lobe graft created by division of the liver along its principal fissure provides an adequate amount of parenchyma, a single bile duct in nearly all patients, and intact common vessels, including the artery, portal vein, and vena cava. Complications of the transected surface are minimal, as we have shown elsewhere,² and the properly used right lobe graft should confer minimal additional risk to the recipient. If the two recipients are very different in size, necessitating the use of the left lateral lobe graft, segment 4 should be removed by a parenchymal dissection without disturbing the integrity of the left portal pedicle. In that way the common left bile duct, left hepatic artery, and left portal vein are available for anastomosis, even though the graft is reduced in size. The pedicle of segment 4 is encountered in the parenchyma and transected well to the right of the round ligament, in that way avoiding any compromise of the biliary structures for segments two and three. This strategy is essential for the performance of left lateral lobe grafts and is applicable for split-liver transplantation and reduced-size transplantation.

The reconstruction of the hepatic vein for the left lobe graft is another area of interest. Although we were not able to document it radiographically, we remain concerned that in using end-to-end left hepatic vein-to-hepatic vein anastomosis the graft is free to move, causing a potential partial obstruction of the hepatic vein outflow. Detrimental effects of even minor elevations in hepatic venous pressure have been demonstrated previously in heterotopic transplant models.^{16,17} Partial hepatic vein obstruction was documented at the time of retransplantation in patient 4L. In patient 9L a vena cava was fashioned using the common trunk of the left and middle hepatic vein, replacing the vena cava of the infant with the middle hepatic vein of the donor.¹⁵ This permits the preservation of a completely intact right lobe graft, as well as the creation of a left lateral lobe graft with a vena cava prosthesis. In this way conventional total hepatectomy

with excision of the vena cava can be performed in the recipient of the left lobe. The fact that the middle hepatic vein and left hepatic vein retain their common fibrous sheath preserving their normal anatomic relationship may prevent kinking and partial obstruction of the outflow of the liver.

The final technical issue is the requirement for portal vein and arterial interposition grafts in the implantation of the left lateral lobe graft. This portal interposition graft, fashioned from the donor iliac vein, is frequently of much larger caliber than the infant portal vein perfusing it, which creates serious flow disparities and led to thrombosis in patient 5L. Because of the flexibility of the portal vein, it has been possible to perform primary anastomosis without interposition graft in three recent cases. It is probably preferable to avoid interposition graft when possible for the portal vein anastomosis. In contrast, however, arterial thrombosis has not been more frequent in split-liver OLT than in full-size OLT, despite the use of iliac artery interposition grafts for left lobe transplants. In fact among children in the present series, arterial thrombosis was more frequent in full-size grafts (10%) than in reduced-size (0%) or split-liver grafts (8%). This compares favorably with an arterial thrombosis rate of 26% observed in a large series of children younger than 10 years old receiving full-sized grafts.¹⁸

What are the constraints to split-liver transplants? Only that neither recipient is imperiled by the procedure. Recipients of the right lobe grafts in reduced-size OLT have an outcome equal to that of full-size liver recipients in our experience,² so with a similar approach that does not include segment 4, the recipient of the right lobe in a split-liver OLT should not be imperiled. Split-liver OLT requires more dissection and the use of vascular interposition grafts for the left lobe as compared to reduced-size OLT. The recently introduced UW preservation solution extends the period that hepatic allografts can be safely stored,¹² minimizing the consequences of the increased time required for graft preparation. Vascular interpositions have been used widely in overcoming a variety of technical problems in hepatic transplantation and do not appear to have conferred increased risk in the present series. Our results indicate that split grafting, while complex, is feasible. Improved results should be realized as more are performed.

An inadequate supply of donors limits the potential usefulness of orthotopic liver transplantation in the pediatric population, particularly small children. Many children with chronic liver disease die while awaiting a donor organ, with most of these deaths occurring in infants. Graft size, urgency of need, and an inadequate supply of donor organs are problems that must be overcome before the full potential of orthotopic liver transplantation in small infants can be realized. Split-liver transplants can

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help to solve them all. This innovation also may be valuable in adults, particularly in urgent conditions.

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Influence of Pentobarbital and Chloralose on Metabolic and Hemodynamic Changes in Liver Ischemia

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Hemodynamic and metabolic consequences of a 90-minute period of liver ischemia followed by 120 minutes of reperfusion were studied in rats that were awake during most of the experiment and in rats anesthetized with either pentobarbital (40 mg/kg body weight) or chloralose (30 mg/kg $\times$ hour) during the complete length of the experiment. Ischemia was induced by occluding the blood vessels to the left and median liver lobes with a small vascular clamp, which was removed after 90 minutes. Protein synthesis rate was determined by measuring incorporation rate of ^{14}C -leucine into protein in incubated liver slices. At the end of the ischemic period, adenosine triphosphate levels in liver tissue and protein synthesis rate were reduced by 80% to 90%, with no significant differences among groups. During reperfusion, energy levels and protein synthesis rate remained depressed in the anesthetized animals, but improved, although not to normal values, in the awake rats. Hepatic tissue water increased during ischemia, probably reflecting hepatocellular membrane injury. The increase in hepatic tissue water was more pronounced in the chloralose group than in the other groups of rats. During reperfusion hepatic tissue water remained increased in the anesthetized rats but was normalized in the awake group. Mean arterial blood pressure was stable during ischemia and reperfusion in the pentobarbital anesthetized rats, while a progressive decrease in blood pressure during the experiment was noted in the chloralose group. The results suggest that hemodynamic and metabolic responses to liver ischemia and reperfusion can be influenced by anesthetics. Chloralose may be less suitable than pentobarbital for anesthesia when liver ischemia is inflicted.

TEMPORARY OCCLUSION OF blood vessels to the liver is often required during operations for major hepatic injury or when extensive resection for tumor is performed.¹ Liver transplantation is inevitably associated with periods of complete ischemia. During liver ischemia, hepatic energy levels are rapidly reduced^{2,3} and impairment of various cellular and subcellular functions

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have been demonstrated, *e.g.*, mitochondrial dysfunction,⁴ reduced protein synthesis,^{3,5-9} and impaired cellular membrane function.¹⁰

The mechanisms of cellular damage in liver ischemia are not fully known.¹¹ During the ischemic period, insufficient supply of oxygen and substrates as well as accumulation of metabolites may all contribute to cell injury, although recent reports suggest that deprivation of oxygen is the single most important factor.¹² Factors implicated in the pathogenesis of postischemic cellular damage include a no-reflow phenomenon, probably caused by cell swelling,¹³ cellular influx of calcium,¹⁴ and oxygen free radicals produced during reperfusion.^{2,9}

Another factor that may contribute to the effects of liver ischemia is the anesthetic agent used during operation. Anesthetic drugs may interfere with the hepatic response to mechanically induced alterations in liver perfusion through multiple mechanisms, *e.g.*, by alterations in regional perfusion pressures and by changes in the vascular tone of the hepatic and preportal vascular beds.¹⁵⁻¹⁹ In addition a direct hepatotoxic effect of different anesthetics has been suggested.

In most studies regarding anesthesia-related effects on liver function, different measures have been used to potentiate the hepatic injury, *e.g.*, pretreatment with phenobarbital and/or exposure to hypoxia. In particular liver injury induced by halogenated anesthetics has been investigated in such models.^{20,21} In previous studies halothane administered during hypoxic conditions to phenobarbital pretreated rats induced hepatic centrilobular necrosis.²² In contrast other halogenated inhalational anesthetics are less noxious and some have even been advocated to exert hepatoprotective effects.²³ The hepato-

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toxic effects of intravenous anesthetics have also been investigated in similar models. For example thiopental and fentanyl induced hepatic injury when administered in association with 10% oxygen.²⁴ Because different anesthetics may impair hepatic function, the choice of anesthesia in experimental models comprising induced liver injury is crucial. The influence of anesthetics on alterations induced by liver ischemia has not been reported previously.

The aim of the present study was to evaluate the influence of pentobarbital and chloralose on changes in regional metabolism and cardiovascular function induced by liver ischemia. We included pentobarbital in the protocol because barbiturate drugs are widely used both in animal experiments and clinical practice. Chloralose was included because of its excellent hemodynamic properties demonstrated in different experimental settings.²⁵ The impact of the anesthetics was gauged by making comparisons with an awake control group of animals, only transiently anesthetized during liver biopsy procedures. For this group enflurane was chosen as the intermittent anesthetic due to its rapid elimination rate and minimal effects on hepatocellular function, even during conditions of pre-existing hepatic injury.²³

Materials and Methods

Male Sprague-Dawley rats weighing 320 to 360 g were fasted with free access to water 24 hours before the experiments, which were started between 8 and 9 A.M. Liver ischemia was induced or sham operation was performed in three groups of rats. In the first group (liver ischemia, $n = 8$; sham operation, $n = 4$), animals were awake during most of the experiments, which lasted for 210 minutes. Short periods of anesthesia were induced with 5% enflurane in oxygen and maintained for 3 to 5 minutes with 2% enflurane in air only to allow the surgical procedures at 0, 90, and 210 minutes (see below). Both animals subjected to liver ischemia and animals undergoing sham operation awoke rapidly after these short periods of anesthesia and showed a normal behavior without evidence of pain between the surgical procedures. In the second group (liver ischemia, $n = 7$; sham operation, $n = 4$), anesthesia was induced with pentobarbital (40 mg/kg body weight) intraperitoneally and maintained during the experiment with supplementary doses of pentobarbital (5 mg/kg) administered intravenously when needed. In the third group (liver ischemia, $n = 10$; sham operation, $n = 5$), anesthesia was induced with methohexital sodium (75 mg/kg) intraperitoneally and maintained by continuous intravenous infusion of chloralose (30 mg/kg $\times$ hour). The rats in the second and third groups were anesthetized during the complete length of the experiments (210 minutes). In these groups a tracheal tube was inserted through a tracheostomy for spontaneous air breathing. The rats were restrained in a supine position

on a warming pad to maintain rectal temperature at 37°C. One jugular vein and one carotid artery were cannulated. Saline (1 mL/hour) was administered as a continuous intravenous infusion with an infusion pump (Sage 335; Sage Instruments, Cambridge, MA) in the pentobarbital group and chloralose was infused in a corresponding volume of saline in the other group. Mean arterial pressure (MAP) was continuously measured with a Bentley Trantec pressure transducer (Bentley Trantec Inc., CA) and a Roche 222 amplifier (Digital Electronics, London, England) operating a Siemens-Elema Mingograph writer (Siemens Elema, Stockholm, Sweden). Acid-base balance and hematocrit were determined in arterial blood at intervals during the experiments in the pentobarbital and chloralose groups. Because the awake animals had no intravenous or intra-arterial lines, blood pressure, hematocrit, and acid-base balance were not measured in these rats.

Induction of Liver Ischemia

Laparotomy was performed *via* a midline incision and the liver hilus was exposed. The blood vessels to the left and median liver lobes were occluded with a small vascular clamp placed distal to the origin of the blood vessels supplying the caudate and right lobes. With this technique approximately 70% of the liver becomes ischemic²⁶ and portal stasis is avoided, which is of special importance for hemodynamic stability in rats.²⁷ The vascular clamp was removed after 90 minutes and the experiments were continued for 120 minutes after start of the reperfusion. In sham-operated animals, the liver hilus was exposed but the blood vessels were not occluded.

Immediately before induction of liver ischemia (0 minutes), at the end of the ischemic period (90 minutes), and 120 minutes after removal of the vascular clamp (210 minutes), small biopsies were taken from the anterior edge of the left and median liver lobes for determination of protein synthesis rate *in vitro*, tissue water, and adenine nucleotides (see below). Complete hemostasis of the biopsy site was usually achieved by gentle pressure with a small sponge for 10 to 20 seconds. Sometimes the biopsy site was sutured with 4-0 catgut. Between the surgical procedures, the abdomen was closed with a running 3-0 silk suture in the first group of rats and with small hemostats in the pentobarbital and chloralose groups.

Hepatic Protein Synthesis In Vitro

Protein synthesis rate was determined from incorporation of leucine into protein in incubated liver slices, as described in detail previously.^{3,6-9} Because the precursor amino acid, ¹⁴C-leucine, was present in the incubation medium at a high concentration (0.58 mmol/L [millimolar]), the extracellular specific radioactivity was used for calculation of incorporation rate. A rapid equilibration

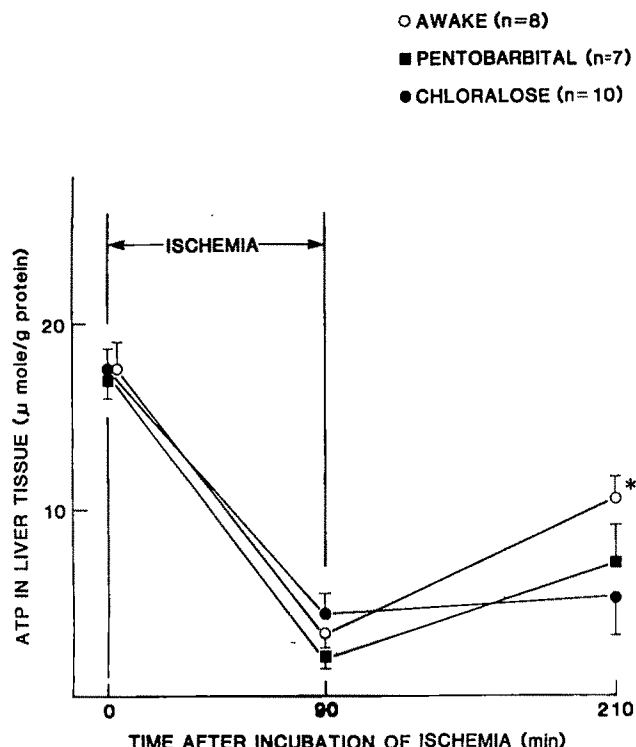


FIG. 1. Adenosine triphosphate in liver tissue. * $p < 0.05$ versus chloralose.

between medium and tissue-specific radioactivities was demonstrated recently under the present *in vitro* conditions, both when slices from ischemic and nonischemic liver were incubated.³

Hepatic Tissue Water

Hepatic tissue water was determined from wet and dry weight and was expressed as liters per kilogram dry weight.

Adenine Nucleotides in Liver Tissue

For determination of adenine nucleotides, liver biopsies were taken with forceps precooled in liquid nitrogen and immediately immersed in liquid nitrogen. The samples were homogenized at 0°C in 300 μ L of 3 mol/L (molar) perchloric acid and neutralized with 800 μ L of 2 mol/L KHCO_3 . After centrifugation, the supernatant was used for fluorometric determinations of adenosine triphosphate (ATP), adenosine diphosphate (ADP), and adenosine monophosphate (AMP).²⁸ The protein content in the pellet was determined according to Lowry et al.²⁹ and the adenine nucleotide levels were expressed as μ mol/g protein.

Statistics

Results are given as mean $\pm$ SEM. Analysis of variance with repeated measurements followed by Tukey's test were used for statistical comparisons.

Results

Adenosine triphosphate levels in liver tissue were reduced by 80% to 90% at the end of the ischemia period, with no significant differences among groups (Fig. 1, Table 1). Changes in ADP and AMP levels were also similar in all groups of rats after 90 minutes of ischemia (Table 1). Energy levels remained depressed during reperfusion, but at 210 minutes, ATP and ADP levels were higher in the awake group than in the pentobarbital and chloralose groups, although the differences were statistically significant only between the awake and chloralose groups. In sham-operated rats, energy levels remained stable during the experiment, with no significant differences over time or among groups (Table 1).

TABLE 1. Adenine Nucleotides (μ mol/g prot) in Liver Tissue of Animals Subjected to Liver Ischemia for 90 Minutes and Reperfusion for 120 Minutes and Anesthetized with Pentobarbital ($n = 7$) or Chloralose ($n = 10$) or Awake Between the Surgical Procedures ($n = 8$)

Metabolite	Ischemia			Sham Operation		
	0 min.	90 min.	210 min.	0 min.	90 min.	210 min.
ATP						
Awake	17.7 $\pm$ 1.1	3.5 $\pm$ 0.7	10.3 $\pm$ 0.9*	17.3 $\pm$ 0.7	17.3 $\pm$ 0.03	ND
Pentobarbital	17.1 $\pm$ 0.7	2.1 $\pm$ 0.2	7.2 $\pm$ 1.1	18.1 $\pm$ 4.1	15.0 $\pm$ 0.4	15.7 $\pm$ 1.2
Chloralose	17.6 $\pm$ 0.9	4.5 $\pm$ 0.7	5.3 $\pm$ 1.8	15.9 $\pm$ 1.3	15.8 $\pm$ 1.3	14.5 $\pm$ 2.1
ADP						
Awake	5.9 $\pm$ 0.8	2.6 $\pm$ 0.7	3.4 $\pm$ 0.3*	5.6 $\pm$ 0.2	6.6 $\pm$ 0.4	ND
Pentobarbital	5.2 $\pm$ 0.4	2.0 $\pm$ 0.3	2.5 $\pm$ 0.5	4.1 $\pm$ 0.4	4.1 $\pm$ 0.4	3.8 $\pm$ 0.2
Chloralose	5.8 $\pm$ 0.1	1.9 $\pm$ 0.3	1.8 $\pm$ 0.4	6.4 $\pm$ 0.5	5.7 $\pm$ 0.6	6.1 $\pm$ 0.9
AMP						
Awake	1.2 $\pm$ 0.3	4.0 $\pm$ 0.4	0.9 $\pm$ 0.3	0.3 $\pm$ 0.04	0.6 $\pm$ 0.03	ND
Pentobarbital	0.3 $\pm$ 0.04	4.4 $\pm$ 0.4	0.5 $\pm$ 0.1	0.6 $\pm$ 0.3	0.3 $\pm$ 0.1	0.3 $\pm$ 0.1
Chloralose	0.6 $\pm$ 0.1	3.9 $\pm$ 0.5	0.4 $\pm$ 0.1	0.4 $\pm$ 0.1	0.2 $\pm$ 0.04	0.7 $\pm$ 0.2

Results from sham-operated animals awake ($n = 4$) or anesthetized with pentobarbital ($n = 4$) or chloralose ($n = 5$) are also shown.

* $p < 0.05$ versus chloralose; ND, not determined.

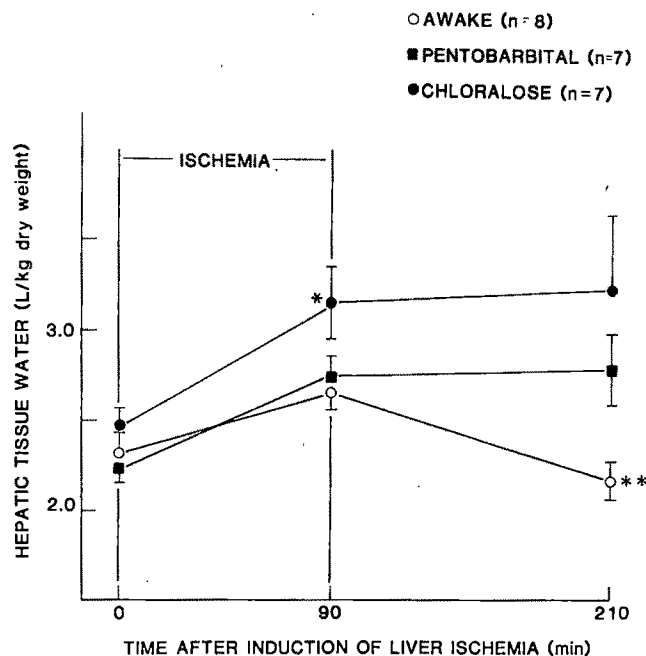


FIG. 2. Hepatic tissue water. * $p < 0.05$ versus awake and pentobarbital; ** $p < 0.05$ versus pentobarbital and chloralose.

Hepatic tissue water increased during the ischemic period in all groups of rats, but the increase was significantly more pronounced in rats anesthetized with chloralose than in the other groups of animals (Fig. 2). Hepatic tissue water remained increased during reperfusion in the pentobarbital and chloralose groups but returned to normal in the awake group (Fig. 2). There were no significant changes in hepatic tissue water over time or significant differences between groups of sham-operated rats (Table 2).

Hepatic protein synthesis rate before induction of ischemia was 0.55 ± 0.05 $\mu\text{mole leucine/g protein} \times \text{hour}$ in the awake group ($n = 8$), 0.72 ± 0.03 $\mu\text{mole leucine/g protein} \times \text{hour}$ in the pentobarbital group ($n = 7$), and 0.89 ± 0.13 $\mu\text{mole leucine/g protein} \times \text{hour}$ in the chloralose group ($n = 10$; no significant differences among groups). At the end of the ischemic period, protein synthesis rate was reduced by 85% to 90% in all groups of rats (Fig. 3). During reperfusion, protein synthesis rate remained depressed in rats anesthetized with pentobarbital or chloralose, while in the awake group, protein synthesis

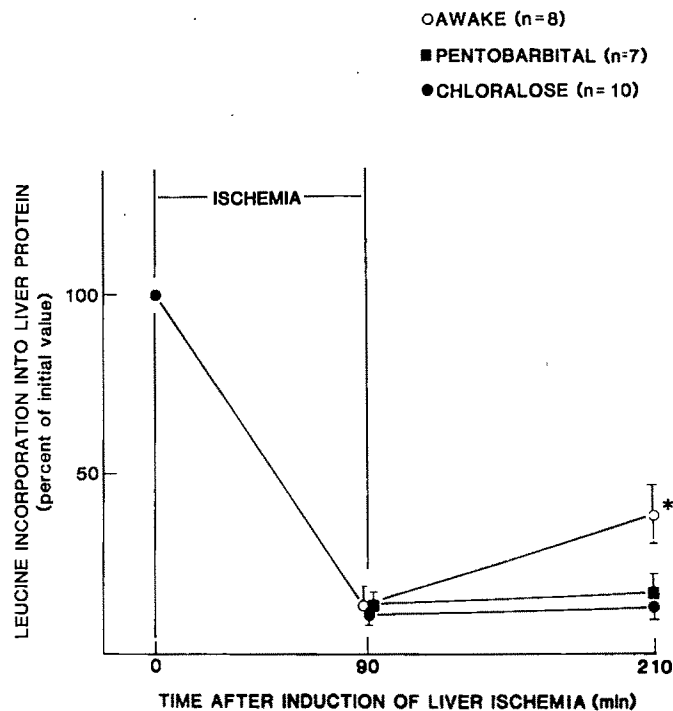


FIG. 3. Hepatic protein synthesis rate. * $p < 0.05$ versus chloralose.

rate improved and was approximately 40% of initial value at the end of the experiment (Fig. 3). No significant changes in protein synthesis rate were noticed in sham-operated animals over time and there were no significant differences among groups (Table 2).

Mean arterial pressure, acid-base balance, and hematocrit were measured only in the pentobarbital and chloralose groups. In the pentobarbital group, MAP remained stable during ischemia and reperfusion (Fig. 4). In contrast there was a progressive decrease in MAP during the ischemic period in the chloralose group, with a further decrease in MAP immediately after reperfusion (Fig. 4). Mean arterial pressure remained lower in the chloralose than in the pentobarbital group during the rest of the study. There were no significant changes in MAP over time and no significant differences among groups in sham-operated rats anesthetized with pentobarbital or chloralose (Fig. 5).

Acid-base balance was stable during the experiments, both in animals subjected to liver ischemia and in sham-operated rats, and there were no significant changes over

TABLE 2. Hepatic Tissue Water (L/kg dry weight) and Protein Synthesis Rate ($\mu\text{mol leucine/g prot} \cdot \text{hour}$) in Sham-operated Rats Anesthetized with Pentobarbital ($n = 4$) or Chloralose ($n = 5$) or Awake Between the Surgical Procedures ($n = 4$)

Experimental Group	Tissue Water			Protein Synthesis Rate		
	0 min.	90 min.	210 min.	0 min.	90 min.	210 min.
Awake	2.44 ± 0.11	2.24 ± 0.08	2.60 ± 0.16	0.43 ± 0.03	0.52 ± 0.06	0.55 ± 0.08
Pentobarbital	2.26 ± 0.13	2.62 ± 0.05	2.43 ± 0.08	0.52 ± 0.05	0.62 ± 0.09	0.46 ± 0.08
Chloralose	2.43 ± 0.11	2.55 ± 0.08	2.60 ± 0.06	0.76 ± 0.17	0.64 ± 0.14	0.54 ± 0.14

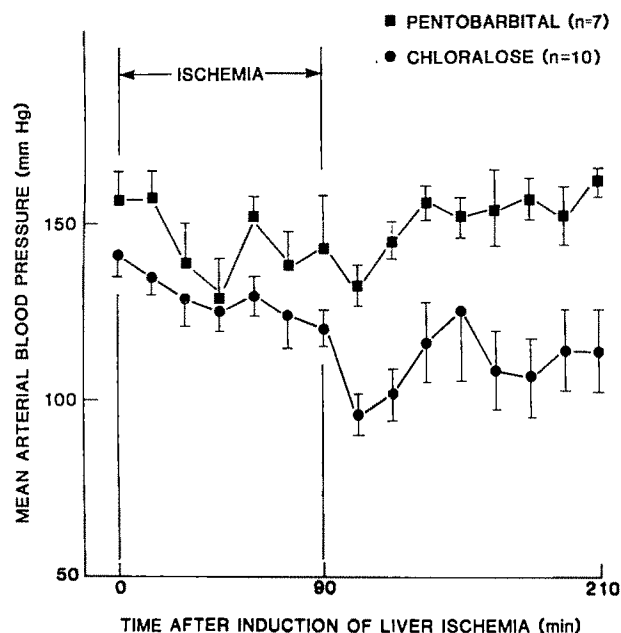


FIG. 4. Mean arterial pressure in pentobarbital and chloralose-anesthetized rats subjected to 90 minutes of liver ischemia followed by 120 minutes of reperfusion. The two blood pressure curves were significantly different ($F = 3.34$; $p = 0.02$).

time or differences between groups in pH, $p\text{CO}_2$, $p\text{O}_2$, or HCO_3^- (Table 3). Hematocrit was somewhat higher in the pentobarbital than in the chloralose group, but no significant changes were noticed over time during the experiments (Table 3).

Discussion

Hemodynamic and metabolic alterations induced by liver ischemia and subsequent reperfusion were studied in rats that were anesthetized with pentobarbital or chloralose or that were awake during most of the experiments. The increase in hepatic tissue water during ischemia was more pronounced in chloralose-anesthetized animals than in the other groups of rats and restitution of protein synthesis, hepatic tissue water, and energy levels during reperfusion was impaired in animals that were maintained under anesthesia during the experiments. The results suggest that the consequences of liver ischemia and reperfusion may be influenced by anesthetics.

An ischemia period of 90 minutes was used to induce severe, but still reversible, hepatic metabolic alterations. In previous studies ATP levels in liver tissue were markedly reduced following 90 minutes of ischemia but improved during reperfusion.² A partial restitution of hepatic cell membrane potential was noted in rats after the same length of ischemia.⁸ Even longer periods of ischemia with subsequent recovery were reported in patients undergoing liver resection¹ and in pigs.³⁰

The present findings of decreased energy levels and reduced protein synthesis rate in ischemic liver tissue correlate with previous reports.^{2,3,6-9} In a recent study from our laboratory a close correlation was observed between protein synthesis rate in incubated liver slices and ATP concentration in liver tissue during ischemia and reperfusion.³ In the same ischemia model, increased hepatic tissue water was caused by both intracellular and extracellular edema,⁹ probably reflecting cellular membrane damage.

Animals in the awake group were briefly anesthetized with enflurane during the surgical procedures and did not have intra-arterial or intravenous lines or a tracheal tube inserted. Consequently these animals were not a clean control group. It is obvious, however, that the present experimental design required anesthesia when liver ischemia was induced and when liver biopsies were taken. Although it is possible that restitution of energy levels and protein synthesis would have been different if the animals had been awake during the complete length of the study, the results in the awake group were probably not affected to a great extent by the short periods of enflurane anesthesia because the drug is rapidly eliminated and has minimal effects on hepatic cellular function, even during conditions of pre-existing hepatic injury.^{23,31,32}

The influence of anesthetics on metabolic events is complex. Administration of different anesthetic drugs can affect the metabolic response to surgical stress³³ and to various pathologic conditions, such as hemorrhage,³⁴ endotoxemia,³⁵ or cerebral ischemia.³⁶ Hepatocellular toxic

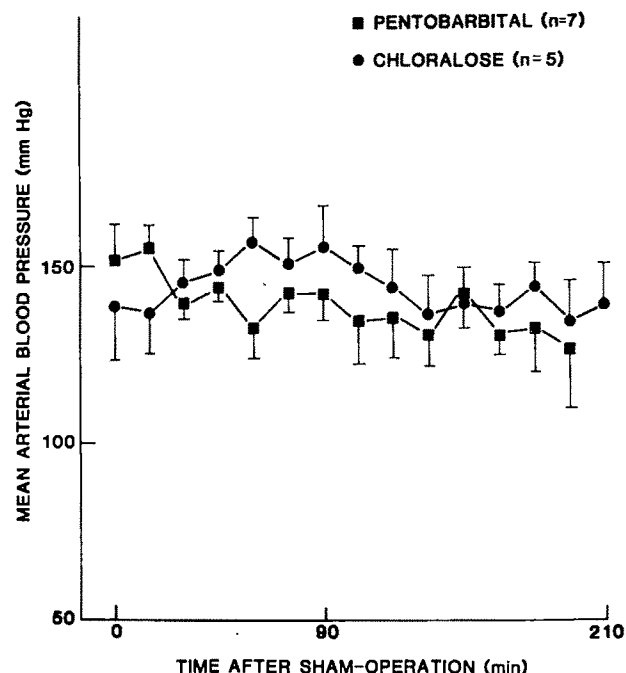


FIG. 5. Mean arterial pressure in sham-operated rats anesthetized with pentobarbital or chloralose.

TABLE 3. Acid-base Balance in Rats Subjected to 90 Minutes of Liver Ischemia, Followed by 120 Minutes of Reperfusion, and Anesthetized with Pentobarbital (n = 7) or Chloralose (n = 10)

Acid Base Balance	Ischemia			Sham Operation		
	0 min.	90 min.	210 min.	0 min.	90 min.	210 min.
pH						
Pentobarbital	7.46 ± 0.02	7.47 ± 0.02	7.49 ± 0.04	7.46 ± 0.03	7.30 ± 0.10	7.48 ± 0.02
Chloralose	7.42 ± 0.02	7.45 ± 0.03	7.44 ± 0.22	7.43 ± 0.02	7.52 ± 0.05	7.53 ± 0.01
pCO ₂ (kPa)						
Pentobarbital	4.0 ± 0.2	3.6 ± 0.3	3.7 ± 0.5	3.3 ± 0.5	3.8 ± 0.3	4.1 ± 0.1
Chloralose	4.4 ± 0.3	4.2 ± 0.3	3.9 ± 0.3	4.1 ± 0.2	3.8 ± 0.1	3.6 ± 0.1
pO ₂ (kPa)						
Pentobarbital	10.9 ± 0.8	12.4 ± 0.8	12.3 ± 0.6	12.2 ± 1.7	10.8 ± 0.2	11.4 ± 1.8
Chloralose	11.4 ± 0.8	10.7 ± 0.5	13.4 ± 0.8	10.4 ± 0.4	13.3 ± 0.4	11.6 ± 1.0
HCO ₃ (mmol/L)						
Pentobarbital	20.6 ± 1.0	19.1 ± 1.5	20.2 ± 0.4	17.1 ± 2.1	16.2 ± 2.7	22.0 ± 1.0
Chloralose	20.5 ± 1.3	20.6 ± 0.5	19.7 ± 2.1	19.8 ± 1.5	22.6 ± 2.0	22.0 ± 0.7
Hematocrit (%)						
Pentobarbital	39 ± 1	39 ± 2	41 ± 1	39 ± 2	41 ± 2	38 ± 5
Chloralose	35 ± 1	36 ± 2	35 ± 4	37 ± 2	37 ± 2	37 ± 2

Results from sham-operated animals, anesthetized with pentobarbital (n = 4) or chloralose (n = 5) are also shown.

effects of inhalation anesthetics or their metabolites³⁷ and microsomal injury caused by lipid peroxidation³⁸ have been described.

In addition to direct metabolic effects, most anesthetics produce hemodynamic changes that can affect tissue function. Several anesthetic drugs reduce liver blood flow and disturb the reciprocal regulation of hepatic artery and portal vein blood flow,¹⁹ and these effects have been implicated in the pathogenesis of metabolic effects of different anesthetics.^{15,16}

Barbiturates typically decrease cardiac output due to depression of cardiac contractility and reduce peripheral vascular resistance. In the rat, however, an opposite peripheral vascular response during pentobarbital anesthesia was recently demonstrated.³⁹ Pentobarbital has been used abundantly in animal experiments, even when hemodynamic stability was considered crucial.⁴⁰ Barbiturates were used in several previous studies on experimental liver ischemia in rats⁶⁻⁹ and did not interfere with hepatic protein synthesis in sham-operated controls.^{6,7} On the other hand, phenobarbital is used frequently for enzyme induction in association with studies on anesthesia-related hepatotoxicity.^{20-22,41-43}

Chloralose is a long-acting anesthetic drug with favorable hemodynamic properties and has been used widely in animal experiments.²⁵ In rats chloralose induced only small cardiovascular deviations from the unanesthetized state⁴⁴ and metabolic, endocrine, and mitochondrial effects of the drug were discrete.⁴⁵⁻⁴⁷ However acidosis after large doses⁴⁸ and a decreased glucose tolerance have been reported.⁴⁹ Hemodynamic and metabolic patterns associated with the use of chloralose in studies of liver ischemia have not been reported before.

The present results suggest that anesthesia with pentobarbital or chloralose aggravates the metabolic conse-

quences of liver ischemia and reperfusion. Because protein synthesis rate, hepatic tissue water, and energy level were not affected by the anesthetics in sham-operated rats, it is likely that the results in the experimental groups reflected the combined effect of liver ischemia and anesthetics. Because the most pronounced deviation from the awake pattern was noticed in rats anesthetized with chloralose, this agent may be less suitable than pentobarbital for anesthesia when liver ischemia is inflicted. This is in contrast with previous findings in rat heart mitochondria, in which chloralose induced fewer alterations than pentobarbital.⁴⁷

The mechanism(s) of impaired cellular function in the postischemic liver of anesthetized rats remains to be determined. Some of our data, however, indicate that hemodynamic effects of the anesthetics may be involved. The higher MAP in rats during pentobarbital than during chloralose anesthesia may reflect increased peripheral vascular tone, as previously demonstrated in rats anesthetized with doses of pentobarbital similar to those used here.³⁹ Such a vasoconstrictor response would maintain blood pressure despite pentobarbital-induced cardiac depression. It may be speculated that increased or maintained regional perfusion pressure in our pentobarbital group improved total liver blood flow after ischemia, resulting in less pronounced metabolic deterioration than in the chloralose-anesthetized rats. Further experiments are needed to test that hypothesis.

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Treatment of Highly Symptomatic Polycystic Liver Disease

Preliminary Experience with a Combined Hepatic Resection-Fenestration Procedure

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Polycystic liver disease (PLD) associated with autosomal dominant polycystic kidney disease is usually well tolerated. However there is a small subset of patients who become incapacitated by massive liver enlargement and for whom effective nonsurgical therapy is limited. Recent surgical advances in the treatment of PLD have raised uncertainties regarding proper management of these highly symptomatic patients. We have reviewed our recent experience with a combined hepatic resection-fenestration procedure to assess its efficacy in nine patients. All patients underwent resection of two or more liver segments and extensive fenestration of residual cysts in the remnant liver. Symptomatic relief and reduction in abdominal girth were obtained in eight surviving patients, persisting for an average follow-up period of 17 months. No progression of cystic disease has been observed clinically or by computed tomography and hepatic function was preserved. Three patients had no complications. Five patients had complications including transient right pleural effusion (3) and thrombosis of an arteriovenous fistula (2). One patient who had a previous hepatic cyst fenestration and a cadaveric renal transplantation died after operation of an intracerebral hemorrhage after experiencing coagulopathy, hyperbilirubinemia, and sepsis. Our results suggest (1) some highly symptomatic patients with massive PLD may benefit from combined hepatic resection and fenestration with acceptable risk, and (2) previous liver surgery and immunosuppressive therapy may increase the risk of such surgery. Longer follow-up is needed in a larger number of patients to determine the duration of benefit from the combined resection-fenestration procedure for highly symptomatic PLD.

MULTIPLE HEPATIC CYSTS or polycystic liver disease (PLD) are frequently associated with autosomal dominant polycystic kidney disease (ADPKD).¹⁻⁵ During the past three decades, medical advances have increased the number of patients with ADPKD who survive long enough to develop severe liver involvement. As experience with such patients has increased, so too has the uncertainty over their proper management. Not infrequently symptomatic patients with PLD exhaust all conservative therapeutic options and

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surgery is considered the next alternative. Our purpose was to determine the value and consequences of combined hepatic resection and cyst fenestration for highly symptomatic patients with polycystic liver disease from our recent experience.

Patients and Methods

We reviewed the medical records of all patients with ADPKD who underwent radical resection for highly symptomatic PLD at the Mayo Clinic from 1985 to 1989. All patients were operated on by a single surgeon (DMN). Information abstracted from patient records included selection criteria, operative technique and extent of surgery, postoperative course, complications, and follow-up.

Patients were selected primarily on the basis of the severity of abdominal symptoms and impairment of clinical performance as estimated by the Performance Status Scale of the American Cancer Society Eastern Cooperative Oncology Group (ECOG). A score of 0 was assigned to unrestricted patients, 1 to patients restricted from strenuous physical activity, 2 to patients capable of self care, 3 to confined patients, and 4 to invalid patients.⁶ Additional indications for operation included infection of one or more hepatic cysts refractory to antibiotics and to percutaneous drainage, regardless of performance status. Hematology, coagulation and chemistry profiles, and nutritional assessment were obtained in each patient. Abdominal computed tomography (CT) scan was performed to delineate cyst distribution, to assess portal vein patency, and to serve as a baseline for follow-up comparison. In addition six patients had an exercise radionuclide cineangiography or a dipyridamole-thallium study to assess cardiovascular performance. Seven patients also had

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evaluation of their cerebral vasculature either by high-resolution computed tomography (CT) scanning or by magnetic resonance imaging (MRI) to detect aneurysmal disease.⁷ If no major medical contraindication to resection was identified, specific hepatic factors were evaluated. Only patients with no major abnormalities of hepatic function tests, a patent portal vein, and relative sparing of two or more adjacent liver segments underwent resection.

Preoperative preparation of each patient included an overnight lavage bowel preparation with oral antibiotics, central venous catheterization, and dialysis or intravenous hydration as indicated. The abdomen was explored through a bilateral subcostal incision. Ascitic fluid was collected, if present, for culture and analysis. The liver was mobilized by division of its peritoneal attachments. The hepatoduodenal ligament was exposed to provide maximal access for vascular inflow occlusion and identification of major vascular and biliary structures. Liver segments spared of cystic involvement were identified before parenchymal transection to define limits to resection. Liver parenchyma and cysts were divided without ligation of hilar vessels or hepatic veins. In fact these structures were often inaccessible to ligation due to liver enlargement. Parenchyma was transected by a modification of the Lin technique with sequential fenestration of cysts along the projected transection plane between diffusely cystic and spared liver.⁸ Using cautery, the transection plane is developed further by division and excision of intercystic septa.⁹ Vascular and biliary radicles that coursed through the cyst septae were suture ligated as indicated. Precise transection through anatomic segmental or lobar planes was precluded due to cystic distortion of normal anatomy. Significant islands of functional liver paren-

chyma were preserved. After resection of major cystic segments, extensive fenestration of residual cysts was performed by excision of the cyst walls. Finally cyst cavities exposed to the peritoneum were fulgurated by electrocautery or by argon beam coagulation (Bard Electromedical Systems, Englewood, CO) in an attempt to ablate secretory epithelium and reduce postoperative peritoneal fluid losses. Cholecystectomy in conjunction with hepatectomy was performed in six patients. The hepatic resection bed was drained by two large closed suction drains.

The Intensive Care Unit (ICU) monitoring was used as necessary. Both colloid and crystalloid were used for volume replacement to compensate for expected postoperative fluid losses and excessive peritoneal drainage. Maintenance of fluid and hemodynamic balance was aided by flow-directed pulmonary artery catheterization and hemodynamic monitoring as necessary. Abdominal drains were removed when drainage volume was not excessive unless previous infection indicated prolonged drainage. Large volume abdominal drainage (3L+) was replaced volume:volume with lactated Ringers and albumin in the immediate postoperative period. Follow-up baseline data included abdominal CT scans and liver function tests at dismissal and three months after operation. In addition four patients had subsequent CT scans from 12 to 36 months after resection. Follow-up at the Mayo Clinic was arranged as medically necessary. The rest of our follow-up was by telephone interview.

Results

Eight women and one man underwent major hepatic resection for highly symptomatic PLD. The clinical features of these patients are summarized in Table 1. Patient

TABLE 1. Clinical Findings of Patients with Polycystic Liver Disease Undergoing a Combined Hepatic Resection-Fenestration Procedure

Patient	Age/Gender	Number of Pregnancies	Oral Contraceptive Use (Years)	Symptoms	ECOG
1	44/F	5	6	Abdominal pain, daily analgesics/narcotics	1
2	35/F	3	6	Abdominal pain, massive distention, early satiety, heartburn, nausea	1
3	43/F	2	6	Abdominal and shoulder pain, early satiety, regurgitation, heartburn	1
4	44/F	5	4	Abdominal pain, massive distention, early satiety, regurgitation, supine dyspnea	1
5	53/F	4	11	Abdominal pain, recurrent fevers, massive distention, early satiety, ascites, uterine prolapse, hemorrhoids	2
6	52/M	—	—	Massive abdominal distention, pain, rib fractures, ascites, dyspnea	2
7	68/F	5	0	Fever, nausea, emesis, pain	2
8	35/F	0	4	Abdominal pain, massive distention, supine dyspnea, heartburn, fatigue, ascites	2
9	50/F	2	15	Abdominal pain, massive distention, early satiety, diarrhea, supine dyspnea, ascites, hypotension during dialysis	2

TABLE 2. Laboratory Findings Before Surgery and at Last Follow-up in Patients with Polycystic Liver Disease Undergoing a Combined Hepatic Resection-Fenestration Procedure

Patient	Before Surgery					Last Follow-up						
	Renal Clearance (mL/min/1.73 M ²)	Serum Creatinine (mg/d L)	Aspartate Aminotransferase (u/L)	Alkaline Phosphatase (u/L)	Serum Bilirubin (mg/dL)	Serum Albumin (g/dL)	Duration of Follow-up (months)	Serum Creatinine (mg/dL)	Aspartate Aminotransferase (u/L)	Alkaline Phosphatase (u/L)	Serum Bilirubin (mg/dL)	Serum Albumin (g/dL)
1	109	0.9	18	167	0.8	4.1	8	0.9	20	137	0.9	3.0
2	74	0.9	16	125	0.8	3.8	36	0.9	25	95	1.0	4.3
3	33	1.8	20	59	0.5	3.9	27	1.8	22	76	0.8	4.3
4	33	1.7	16	146	0.6	3.8	27	2.0	15	121	0.4	3.9
5	Dialysis	Dialysis	13	208	0.4	3.3	18	Dialysis	14	208	0.3	3.5
6	34*	1.6*	35	339	0.8	3.6	—	—	—	—	—	—
7	—	1.4	31	551	0.5	2.9	12	2.2	21	292	0.5	4.1
8	68	0.9	28	159	0.6	2.7	4	0.9	32	192	0.3	4.0
9	Dialysis	Dialysis	14	201	0.7	3.3	2	Dialysis	14	196	0.6	3.7
Normal Range	80-120	0.7-1.1	12-31	70-196	≤1.1	3.5-5.0						

* Cadaveric renal transplant.

age ranged from 35 to 68 years and averaged 47 years. All women had either multiple pregnancies or had taken oral contraceptives. Specific symptoms included pain, massive abdominal distention, early satiety, nausea, regurgitation, heartburn, supine dyspnea, diarrhea, uterine prolapse, and hemorrhoids. Two patients had clinical evidence of cyst infection but only one patient had positive cyst fluid cultures. Three patients had clinical evidence of ascites and one hypotension during dialysis. Clinical performance status was impaired in each patient and was assessed as ECOG performance score 1 in four patients and 2 in five. The duration of disabling symptoms averaged 56 months, ranging from 8 to 144 months. Liver function tests were essentially normal, except for mild elevation of serum AST and alkaline phosphatase in one and four patients, respectively, and hypoalbuminemia in four (Table 2). Renal function was normal or relatively spared (serum creatinine less than 1.8 mg/dL) in six patients. Two patients required chronic hemodialysis and one patient had reduced but stable renal function 2 years after right nephrectomy, hepatic cyst fenestration, and cadaveric renal transplantation. Two other patients had previous abdominal explorations; one patient had a splenectomy and, on a separate occasion, an exploration only for a ruptured hepatic cyst, and another patient had transabdominal fenestration of left renal cysts.

All patients underwent multisegmental hepatic resection. Two to six liver segments were excised in each patient (Table 3). An example of a massively enlarged polycystic liver with segmental sparing before and after resection-fenestration is shown in Figure 1. The weights of the pathologic specimens ranged from 911 to 7600 grams and averaged 2869 grams. Because fluid was aspirated during cyst fenestration in each patient, the weight of the resected liver underestimated the net loss of mass in each patient. Weight loss during hospitalization ranged from 1.8 to 17 kg, with a mean of 6 kg. Six patients had a cholecystectomy and one had ligation of a splenic artery aneurysm and fenestration of multiple right renal cysts.

The average length of hospitalization was 15 days, with a range of 7 to 34 days and a median of 13 days. Six patients required intensive care, specifically for overnight observation of hemodynamics alone in 4 patients, 6 nights in 1, and 32 nights in the remaining patient.

The average duration of drainage was 13 days, with a range of 6 to 32 days. In eight patients abdominal fluid drainage varied from 10 to 5725 cc daily. Drainage exceeded 3000 cc per day for 8 consecutive days in one patient. Drainage was prolonged intentionally in patients with preoperative cyst infection despite low volume output. Furthermore two patients on hemodialysis had prolonged, high-output drainage. Both of these patients had ascites after operation that gradually decreased in clinical significance. Volume and protein losses from peritoneal

TABLE 3. Extent of Resection, Transfusion Requirements, Morbidity and Mortality, and Relief of Symptoms Undergoing a Combined Resection-Fenestration Procedure in Patients with Polycystic Liver Disease

Patient	Hepatic Segments Resected	Blood/RBCs (units)	Duration (days)		Complications	Pain Relief	Abdominal Girth
			Drains	Hospitalization			
1	VII, VIII	2	6	7	None	↓	↓
2	VII, VIII	2	8	9	Right pleural effusion	↓↓↓	↓↓↓
3	VII, VIII	8	10	11	Right pleural effusion	↓↓↓	↓↓↓
4	II-VI, VIII	4	9	12	None	↓↓↓	↓↓↓
5	II, VII, VIII	8	14	16	Thrombosis of AV fistula	↓↓↓	↓↓↓
6	II, VI-VIII	61	32	34	Hypotension, coagulopathy, cholestasis, cerebral hemorrhage, death	—	—
7	V, VI-VIII	8	11	13	None	↓↓↓	↓↓↓
8	IV-VIII	6	13	14	Right pleural effusion	↓↓↓	↓↓↓
9	I-IV, VII, VIII	6	17	21	Thrombosis of AV fistula	↓↓↓	↓↓↓

Reduction of pain or girth: marked ↓↓↓, moderate ↓↓, minimal ↓.

drainage required careful monitoring and prompted infusion of a lactate Ringers solution and albumin to maintain fluid and protein balance.

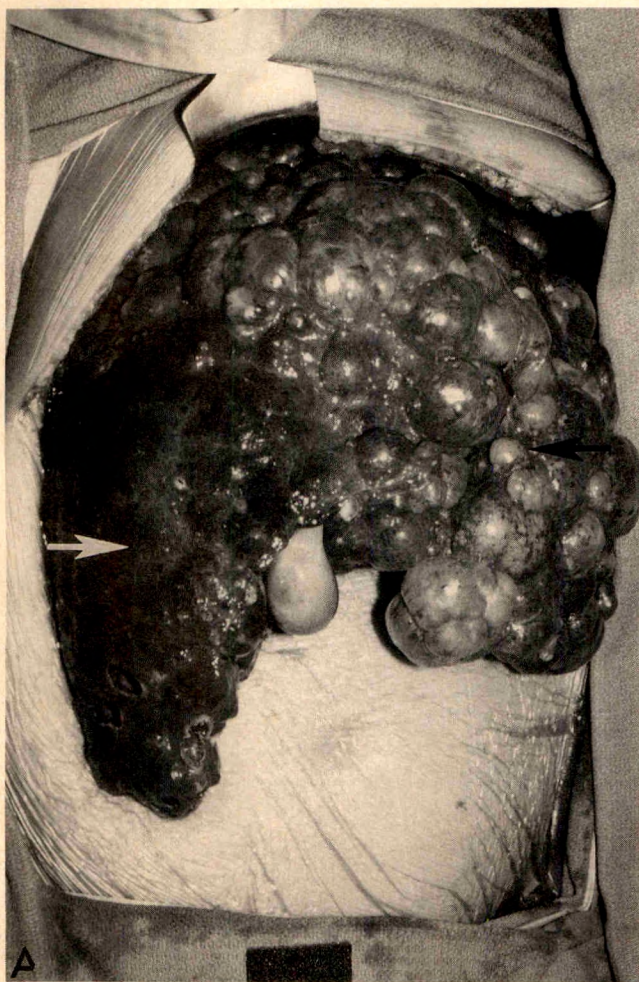


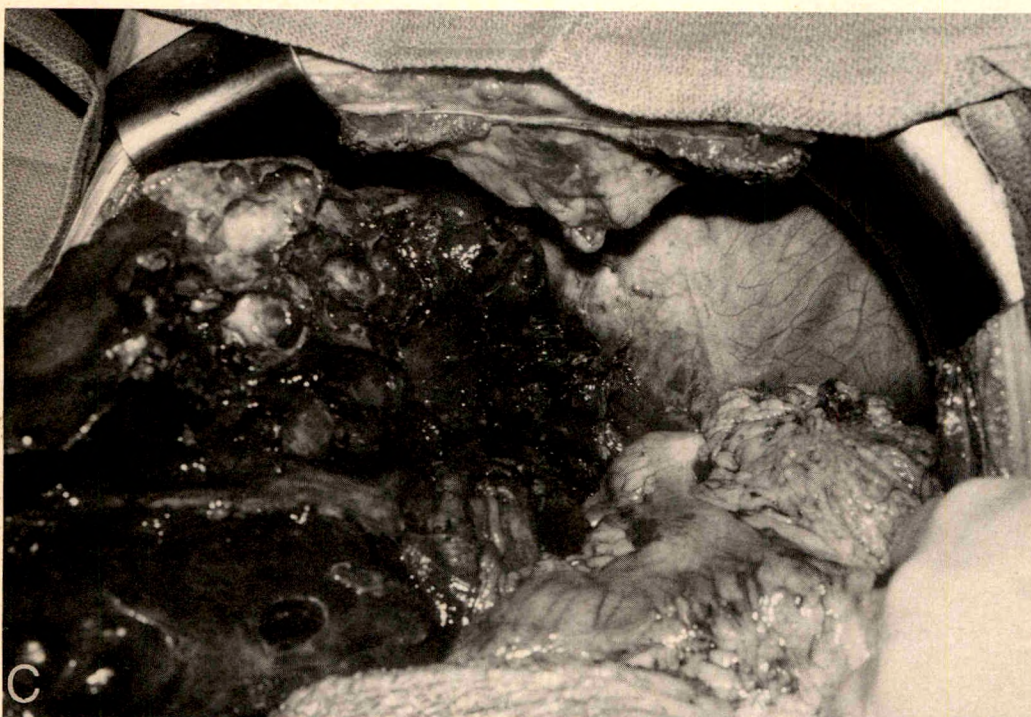
FIG. 1A. Intraoperative photographs of massively enlarged polycystic liver, showing polycystic liver (black arrow) and spared parenchyma (white arrow).

Blood components were transfused intraoperatively and during hospitalization in each patient. The median transfusion of packed red blood cells (PRBC) was 6 units, with a range of 2 to 61 units. One patient consumed 61 of the total 105 units transfused in our series. Another patient used the majority of her eight units in the course of vascular access revision and dialysis.

Three patients had a completely uncomplicated course. Three patients had transient right pleural effusions. Only one patient required thoracentesis. Two patients on dialysis had perioperative thrombosis of their arteriovenous fistula and required reconstruction of a new vascular access for dialysis.

Patient six had undergone previous hepatic cyst fenestration and renal transplantation and was receiving chronic immunosuppression. He had the most extensive liver involvement without sparing of two adjacent liver segments and required preoperative correction of malnutrition. His resection was complicated by intraoperative hemodynamic instability and consumptive coagulopathy. Transient hyperbilirubinemia and two episodes of sepsis complicated his postoperative course before his death due to an intracerebral hemorrhage. Although the death was presumed secondary to a ruptured berry aneurysm, an aneurysm was not confirmed at autopsy.

All surviving patients have experienced relief of abdominal symptoms and have returned to a normal performance status that has persisted for an average period of 17 months, with a range of 2 to 44 months of follow-up. Abdominal girth was reduced markedly in five patients, moderately in two, and minimally in one. The degree of abdominal girth reduction was related to the extent of resection, which increased as our experience grew. Reduction in liver size and abdominal girth was confirmed radiographically in all patients. Repeated abdominal CT scans in these patients have failed to show significant development of cysts in the previously spared liver segments during a mean follow-up period of 24 months. Indeed, as



FIGS. 1B and C. (B) Anticipated transection plane between spared and polycystic liver (double black arrow). (C) Remnant liver after left hepatectomy. Resection of cystic segments 7 and 8 was subsequently completed.

shown in Figure 2, CT scans have confirmed postresection hypertrophy of the spared liver and lack of clinically significant cyst progression. Liver function tests have remained stable (Table 2). Patient acceptance of the procedure has been considered good by seven patients responding favorably to questions of procedure worth and

continued willingness to recommend the procedure based on their experience.

Discussion

Polycystic liver disease frequently develops in patients with ADPKD. Estimates of the prevalence of hepatic cysts

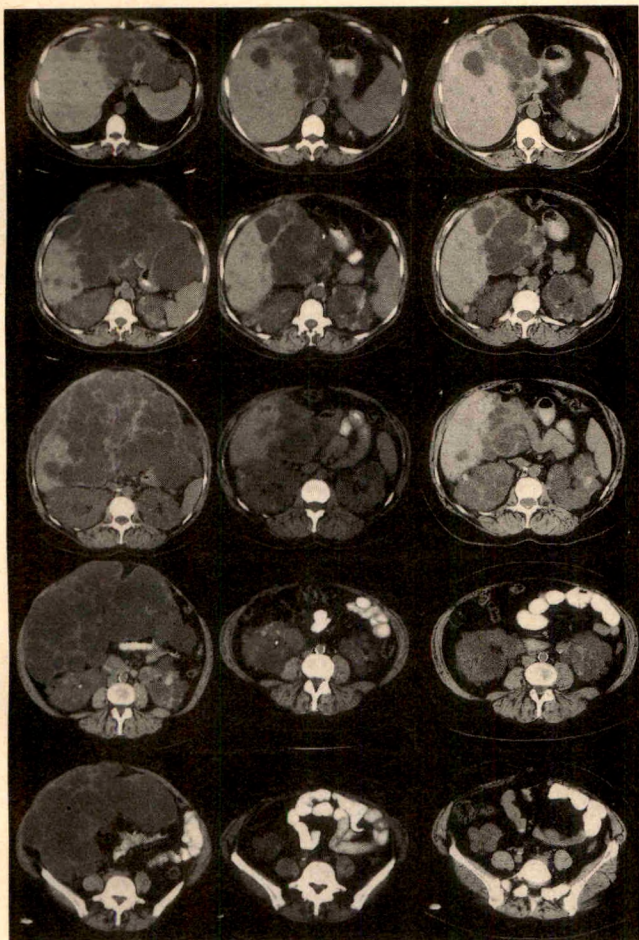


FIG. 2. Computed tomography of the abdomen in a patient with PLD before (left panels) and 3 months (central panels) and 3 years after (right panels) the combined resection-fenestration.

at autopsy have varied from 48% to 55% in patients with ADPKD.^{1,2} Recent studies using ultrasonography and CT for liver imaging have confirmed an increased prevalence, which approached 100% in studies of long-term survivors after renal transplantation.^{10,11} Risk factors associated with the development of polycystic liver disease in patients with ADPKD include increasing age, female gender, gravidity, and degree of impairment of renal function.^{1-3,5,12,13} Despite this prevalence, hepatic cysts rarely cause symptoms or affect liver function. Indeed before renal transplantation, complications from renal cysts were the primary source of symptoms and death in patients with ADPKD.^{1,2} As the treatment for chronic renal failure improved, survival of patients with ADPKD increased and, consequently, profound hepatocystic disease has become increasingly significant. Symptoms or complications from hepatic cysts are more frequent and a recent study of 229 patients with ADPKD has shown that 10.5% of deaths were from complications arising in hepatic cysts.¹⁴

Symptoms arise in patients with PLD from liver enlargement and compression of adjacent structures. Most

symptomatic patients complain of increasing abdominal girth and a chronic dull abdominal pain. Liver enlargement may cause early satiety, weight loss, respiratory compromise, and physical disability.^{13,15-21} Clinical performance status deteriorates and gross change in body habitus may become both physically and psychologically incapacitating. Acute severe pain may accompany cyst rupture or intracystic hemorrhage. Infection of hepatic cysts, especially in patients on chronic dialysis or in patients immunosuppressed after renal transplantation, may produce either subclinical or overt sepsis.²²⁻²⁵ Portal hypertension,²⁶⁻²⁸ obstructive jaundice,²⁹⁻³³ and malignant degeneration^{34,35} are rare complications. Hepatic failure in the polycystic patient has been reported very rarely.^{27,36}

Nonsurgical treatment options for the few patients with incapacitating symptoms have been limited. Preliminary observations that hepatic cyst epithelia are sensitive to hormones that have an effect on the biliary system (*e.g.*, secretin) suggest that the natural history of these cysts might be influenced pharmacologically.³⁷ Whether reduction in extant cysts could be expected from hormonal therapy is unknown. Paliard *et al.*³⁸ found that cimetidine reduced the secretion rate of unroofed cysts, possibly by inhibiting gastric acidity and thus secretin-induced secretion. For patients who have only a few dominant cysts, percutaneous drainage has provided temporary relief.³⁹ Subsequent sclerosis using 95% ethanol or pantopaque has reputedly prolonged the relief afforded by percutaneous drainage.⁴⁰⁻⁴²

Simple cyst fenestration and peritoneal marsupialization have been the mainstays of surgical therapy. Fenestration had produced incomplete or temporary pain relief but rarely documented reduction in abdominal girth. Lin *et al.*⁸ reported a more extensive fenestration procedure in three patients with PLD in whom successively deeper cysts were unroofed and drained through more superficial ones, resulting in significantly decreased hepatic symptoms. van Erpecum *et al.*⁴³ reported nine patients who underwent the Lin fenestration procedure. Although one patient died from hemorrhagic shock, abdominal complaints resolved in seven of the eight surviving patients. Furthermore obstructive jaundice and esophageal varices resolved in three of these patients. Howard *et al.*²⁹ also have reported resolution of biliary obstruction in one patient after Lin decompression. In practice, however, the efficacy of the Lin decompression for PLD is limited by extent of cysts, access to central cysts, postoperative walling off of cysts, and the rigid architecture of the fenestrated liver, which does not completely collapse.

For isolated cyst complexes, resection of the involved liver has been advocated.⁴⁴⁻⁴⁶ Iwatsuki and Starzl⁴⁷ described two patients with extensive PLD who underwent right trisegmentectomy and right hepatectomy, respectively. Both patients had symptomatic relief.

In 1984 Armitage and Blumgart⁹ reported one patient in whom sequential fenestration and resection were combined. Symptoms resolved and abdominal girth was reduced significantly. Their patient remained well during the 1-year follow-up period. The key modification by Armitage and Blumgart was that successive fenestration along a projected plane between diffusely cystic and spared parenchyma allowed safe resection of nonfunctioning symptomatic cystic mass with preservation of liver function. Thus the extent of fenestration was reduced and diffusely cystic volume was excised. Turnage et al.⁴⁸ reported three patients who also underwent combined resection-fenestration. Two of three patients had left lateral segmentectomies and one had a left lobectomy. Two of these patients died and consequently they reserve combined resection-fenestration for highly selected patients incapacitated by PLD. If the distribution of liver cysts in other patients with ADPKD would allow application of this combined technique, a realistic surgical option for highly symptomatic patients could be developed. Recently we reviewed abdominal CT scans from 119 patients with ADPKD and found massive liver involvement in 6 men and 18 women.¹⁵ Twenty-one of these patients had relative sparing of two or more adjacent liver segments, thus confirming that resection is anatomically feasible in most patients.

Our experience with combined hepatic resection and fenestration shows that some patients with massive polycystic liver disease benefit markedly from this procedure. As our experience grew, we have performed extended hepatectomies in four patients. Our mortality and morbidity rates have been limited. Previously five patients have reportedly undergone major hepatic resection, *i.e.*, resection of more than three liver segments.^{9,47-49} Careful identification of patients who have hepatic anatomy amenable to resection is imperative for the combined resection-fenestration. We used extensive preoperative evaluation to identify potential risks contraindicating resection by excluding patients with hepatic insufficiency, suspected malignancy, or significant cardiopulmonary compromise. Patients with malnutrition underwent preoperative correction to optimize nutritional status.

Two conditions may increase the operative risk of combined resection-fenestration for PLD. Previous abdominal surgery with abdominal adhesions between the liver and other viscera posed technical difficulties. In particular previous cyst fenestration resulted in more intense intra-abdominal adhesions. Therefore we advise patients with a history of previous surgery of the additional risks of bleeding or enterotomies. As a corollary we advocate cholecystectomy during hepatectomy to eliminate potential confounding diagnostic problems of postoperative biliary tract disease and to obviate the risk of subsequent cholecystectomy. Similarly we question whether a fully

immunosuppressed patient should undergo major liver resection because of the complicated course of our only patient who had a functioning renal allograft. We could not determine which aspects of his medical history (extent of liver involvement, immunosuppression, previous liver surgery, cyclosporin A use, nutritional status) contributed primarily to his death. Interestingly coagulation abnormalities have been described in relation to cyclosporin A use, including microangiopathic hemolytic anemia and consumption coagulopathy.⁵⁰ None of the previously reported five patients who have undergone similar resections had comparable risk factors,^{9,47,48} although one patient described by Turnage et al.⁴⁸ who had undergone previous liver surgery suffered a similar postoperative course.

Whether combined hepatic resection-fenestration should be used in patients with symptomatic PLD and concurrent renal failure is not clear. Although we have operated on two such patients, morbidity was greater in these patients than in our patients without renal failure. Combined single donor hepatic and renal transplantation offers an alternative solution to such patients. Clearly combined transplantation is indicated if both hepatic and renal failure are present. However hepatic failure is rare. We have been reluctant to advocate combined transplantation because liver-related symptoms can be effectively treated by resection-fenestration with preservation of normal liver function. Whether hepatic transplantation will ever be necessary in such patients is uncertain. Clearly current data supporting either treatment option is insufficient to recommend one preferentially. Follow-up studies examining the rate of cyst progression after resection and the early and late risk of allograft rejection from either sequential or combined multiorgan transplantation is needed.

The long-term benefit of combined hepatic resection and fenestration will be determined by postoperative progression of cystic degeneration in the spared liver remnant. Current data of the natural history of ADPKD and PLD suggest that progression of cystic disease will be slow, affording the possibility of prolonged benefit.¹⁻⁵ Although our follow-up is limited, clinical progression has not occurred in any of our patients. In contrast Iwatsuki and Starzl⁴⁷ observed cystic progression in two patients, 8 and 9 years after partial hepatectomy. We fully agree that hepatic transplantation should be used for disabling symptoms from progression of PLD after resection. Primary hepatic transplantation for PLD should be used preferably in patients without liver sparing or in rare patients with liver failure.

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Breast-conserving Therapy for Macroscopically Multiple Cancers

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Of 586 unilateral stage I-II breast cancers treated with conservative surgery and radiotherapy, 61 patients were found to have two or more macroscopic tumor nodules, diagnosed either clinically ($n = 20$), mammographically ($n = 2$), or on gross pathologic examination ($n = 39$). After a median follow-up of 71 months, 15 of 61 (25%) of the patients with multiple tumors developed recurrence in the treated breast, compared to 56 of 525 (11%) of patients with single cancers ($p < 0.005$). Local failure occurred in 6 of 37 (16%) of bifocal tumors and in 9 of 24 (35%) of patients with 3 or more tumor foci. Recurrence was more frequent for multiplicity diagnosed clinically or mammographically (8 of 22 patients, 36%) than when it was apparent only to the pathologist (7 of 39 patients, 18%). Only 1 of 21 bifocal tumors diagnosed on gross examination recurred. Local failure occurred in only 1 of 22 cases with clearly negative resection margins; the remaining recurrences were associated with positive ($n = 3$) or indeterminate margins ($n = 11$). In contrast with recurrences of unifocal breast cancers, local failures in these patients tended to be located at a distance from the original foci, to be multifocal, or to be diffuse, including skin involvement. Only four recurrences presented as a single focus in the vicinity of the original primary tumors. This study indicates that macroscopically multiple breast cancers are at higher local failure risk, especially if multiplicity is clinically apparent, or if three or more gross nodules are seen on pathologic examination. Negative resection margins appear to be essential for satisfactory results.

ALTHOUGH MULTIPLE PATHOLOGIC studies attest to the multifocality and multicentricity of many breast cancers,¹⁻⁶ the appearance of two or more dominant tumor masses in the same breast is very uncommon.⁷ Such patients are commonly excluded from breast-conserving treatment programs under the assumption that patients with macroscopically multiple tumors have a high risk of local recurrence.⁸ Data to support this attitude, however, are lacking.

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At the Marseille Cancer Institute, patients with two or more tumor nodules have not been denied systematically treatment with preservation of the breast. This affords the unusual opportunity to analyze treatment results for this small subset of patients, for whom breast conservation is considered in many centers to be contraindicated.

Methods

The study group includes 586 evaluable patients with clinical stages I and II breast cancer (T1-2 NO-1, American Joint Committee,⁹) whose primary surgical treatment took place at the Marseille Cancer Institute between January 1975 and December 1983. Patients operated on outside the Cancer Institute and referred for radiotherapy, patients with clinical stage III or IV cancer, and patients treated by primary mastectomy were excluded.

Surgical and radiotherapy techniques, as well as the results of therapy, have been described in detail in previous publications.¹⁰⁻¹² Conservative surgery consisted of a macroscopically complete wide excision of the primary tumor, including in 486 instances a dissection of the lower two axillary levels. No particular attention was paid to microscopic resection margins, and re-excision was not used. Megavoltage radiotherapy involved treatment of the entire breast and draining lymph node areas to a basic dose of 50 Gy (5000 rad) in 5 weeks with telecobalt or 60 Gy in 6 weeks with telecesium. The tumor bed always received supplemental treatment, usually 20 to 25 Gy with an external electron beam. Adjuvant therapy did not follow a fixed protocol during the 9-year period of this study. Bilateral oophorectomy or hormone therapy was per-

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formed on 212 patients, and 88 patients were treated with combination chemotherapy. In addition almost all patients treated after January 1980 received a short perioperative course of single alkylating agent.

The clinical records and pathology reports of all patients were examined and histologic slides of all primary tumors were reviewed by a single pathologist (JJ) who had no knowledge of the clinical outcome. Histologic tumor type was assigned according to the World Health Organization,¹³ with infiltrating cancers classified by their predominant invasive component. Tubular carcinomas were included in the category invasive ductal carcinoma (IDC). The degree of intraductal cancer was quantified using the terminology of Schnitt et al.¹⁴ Extensive intraductal component (EIC) was considered present only when at least 25% of the tumor mass consisted of ductal carcinoma *in situ* (DCIS), and at the same time DCIS was present in the surrounding breast tissue. Histologic grade was assigned according to a modified Bloom-Richardson system.¹⁵

Although no prospective India ink marking of resection margins had been performed, pathologic review included a retrospective assessment of the adequacy of excision. In addition to sections through the primary tumor, in most cases selected sections had been taken at the periphery of the excision specimen. Excision was considered to have been complete when sections through tumor showed no invasive or intraductal cancer at the margins and the peripheral sections were free of tumor. Excisions in which such a judgment could not be made, particularly when no peripheral sections were available for review, were classified as indeterminate. About 10% of cases had clearly positive margins.

Tumors were considered to be macroscopically multiple when either the preoperative clinical and/or mammographic examination showed more than one discrete tumor mass or when the pathologist, on gross examination, found two or more tumor nodules separated by apparently non-neoplastic tissue. Tumors in which multifocality was apparent only on microscopic examination were classified as unifocal cancers.

Statistical analysis was based on proved recurrence in the parenchyma or skin of the treated breast, without consideration of previous events. Both direct ratios and actuarial survival functions¹⁶ were used; differences between proportions were tested by the chi² test, and between survival functions by the log-rank test.¹⁷ Multivariate analysis used the computer program Survival Analysis with Covariates—Cox Models (BMDP Statistical Software, Los Angeles, CA).

Results

Sixty-one of the 586 (11%) patients were found on review to have had macroscopically multiple tumors. In 20

patients two or more separate nodules were apparent on clinical examination and were confirmed pathologically. In 10 instances the nodules, although discrete, were in close proximity, so that a standard wedge excision could be performed.¹² In 10 patients the foci were separated by a considerable distance, so that either separate incisions or a generous partial mastectomy were required. Mammography alone detected a second focus at a distance from the primary tumor in two patients. Of the 22 multifocal tumors diagnosed clinically or mammographically, 15 were bifocal and 7 were trifocal. In the remaining 39 cases, multifocality was apparent only to the pathologist on gross examination. In 21 instances the tumor was macroscopically bifocal, and in 18 cases more than 2 separate nodules were identified (3 in 11, 4 in 4, more than 4 in 3). In all cases the nodules were in close proximity to each other.

Pathologic review showed the predominant histologic pattern of infiltrating ductal carcinoma in 54 of the 61 patients with multiple tumors (88.5%), in comparison to 442 of 525 patients with unifocal tumors (84%, difference insignificant). Of patients with IDC, 17 (31.5%) had EIC. The remaining 7 patients had infiltrating lobular cancer (n = 3), DCIS (n = 3), and colloid carcinoma (n = 1). Significant differences in histologic type between tumor nodules in individual patients were not seen.

Table 1 compares the characteristics of patients with macroscopically multiple tumors to those having grossly unifocal cancers. Although EIC was observed more frequently in multifocal tumors, no significant differences could be demonstrated in the frequency or extent of nodal

TABLE 1. Comparison of the Characteristics of Patients with Macroscopically Multiple Versus Grossly Unifocal Tumors

Characteristic	Single	Multiple	p value
Number	525	61	
Mean age (years)	52	50	NS
Histology			
Invasive ductal	442 (84%)	54 (88.5%)	NS
With EIC	89 (20%)	17 (31.5%)	0.06
Other	83	7	
Estrogen receptor			
≥10 fm/mg	308 (59%)	39 (64%)	NS
<10 fm/mg	140	12	
Unknown	77	10	
Involved nodes			
None	257 (49%)	37 (52.5%)	NS
1-3	128	15	
4+	47	7	
Unknown	93	7	
Resection margins			
Adequate	288 (55%)	22 (36%)	0.01
Inadequate	30	12	
Indeterminate	207	34	
Local recurrence	56 (11%)	15 (25%)	0.005
Contralateral cancer	22 (4%)	2 (3%)	NS
10-year survival	74%	73%	NS

NS, not significant.

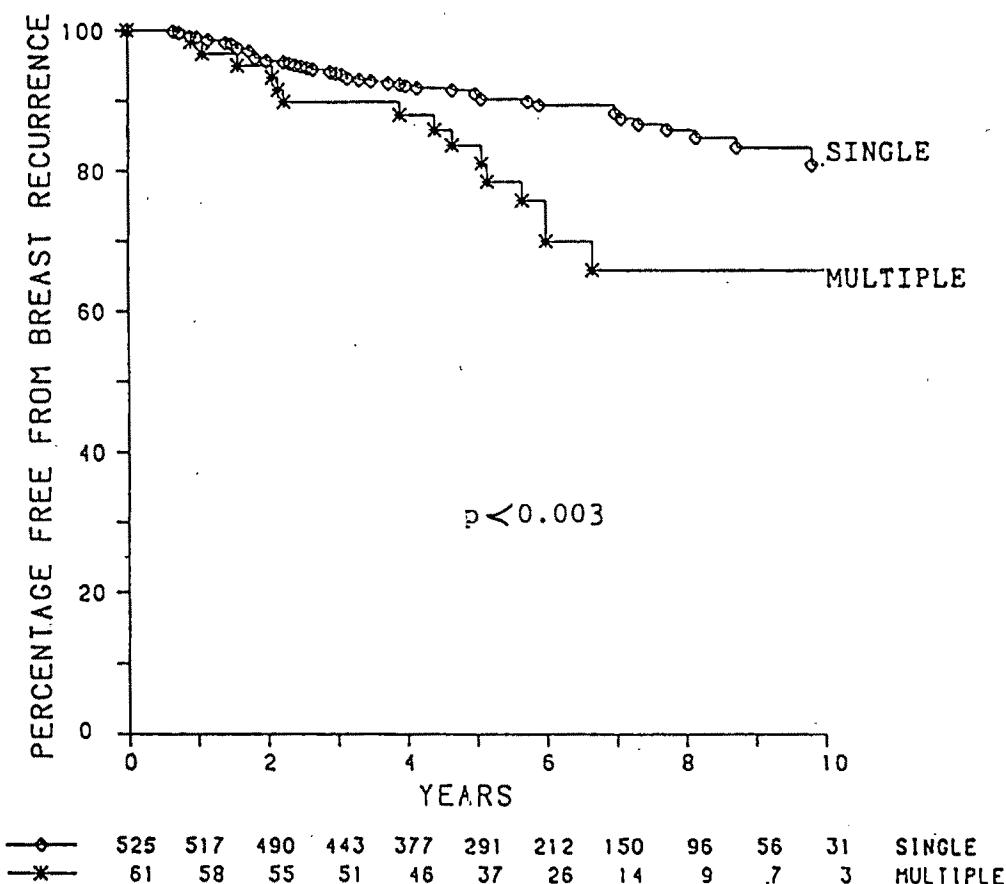


FIG. 1. Actuarial freedom from local recurrence in the treated breast for patients with macroscopically multifocal versus unifocal tumors. The numbers below the time axis indicate the patients at risk for each interval.

involvement or in estrogen receptor status. Microscopically adequate resection margins, however, were achieved more frequently for unifocal than for multifocal tumors. The overall survival rate was the same for both groups.

After a median follow-up of 71 months, 15 of the 61 patients (25%) with multifocal tumors developed recurrence in the treated breast, compared to 56 of the 525 (11%) patients with unifocal cancers ($p < 0.005$). Actuarial local recurrence-free survival curves for the two groups are shown in Fig. 1. Local failure occurred in 6 of 37 (16%) bifocal tumors and in 9 of 24 (37.5%) patients with 3 or more tumor foci ($p = 0.1$). When multiplicity had been apparent clinically or mammographically, local relapse occurred in 8 of 22 patients (36%), regardless of whether the tumor foci were close together (4 of 10 recurred) or far apart (4 of 12 recurred). Multifocality diagnosed only on gross pathologic examination led to local failure in 7 of 39 instances (18%, $p > 0.1$). Only 1 of 21 bifocal tumors diagnosed by the pathologist recurred in the breast. However, when 3 or more nodules were apparent on gross examination, 6 of 18 (33%) developed local failure. Based on the clinical and gross pathologic examination, therefore, excess local recurrence risk appeared to be confined to the 46 cases in which multifocality was either apparent to the clinician, or in which 3

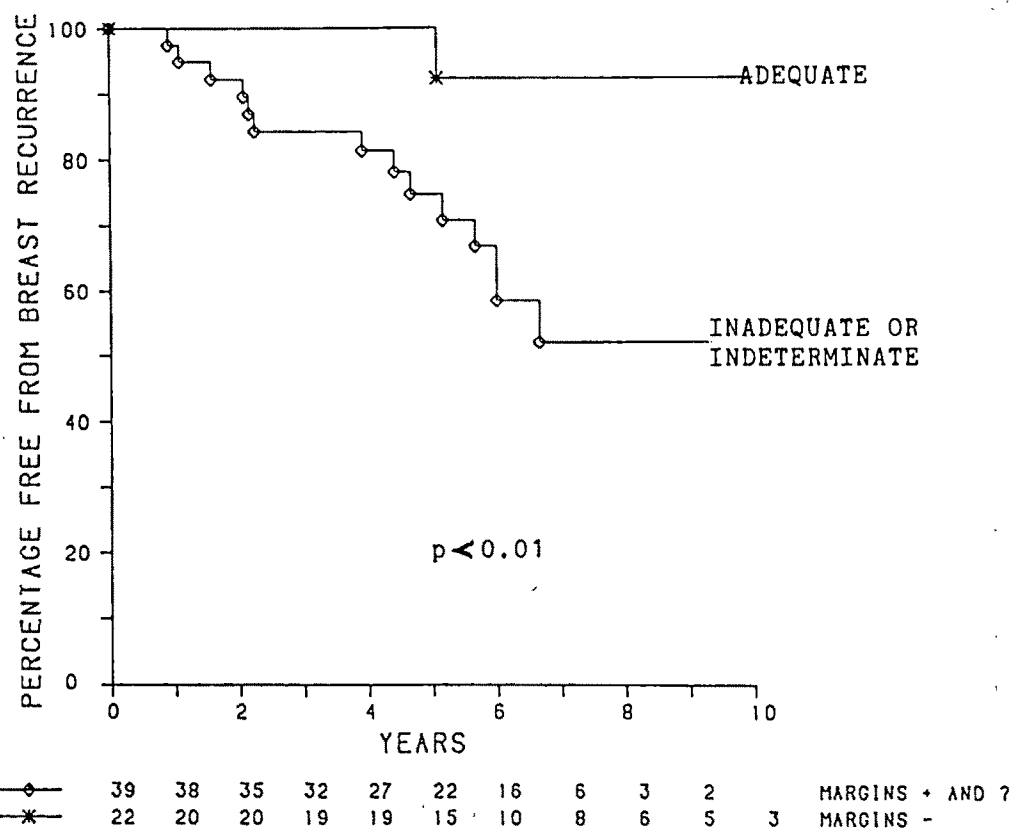
or more gross nodules were observed by the pathologist ($p < 0.025$ compared to the 21 pathologically bifocal tumors).

The influence of the microscopic examination on local recurrence risk was investigated for the 61 patients with macroscopically multiple tumors. All but one of the 15 local failures occurred in tumors showing predominantly invasive ductal histology. Local recurrence was observed in one of three patients with invasive lobular cancers, and in none of the four patients with other histologic tumor types. For patients with IDC, multiple tumors showing EIC had a tendency to recur more frequently (6 of 17, 35%) than those without EIC (8 of 37, 22%), but this difference was not statistically significant ($p > 0.1$).

The adequacy of resection could be judged with confidence in 34 instances, and in 27 cases resection margins were classified as indeterminate. Whereas local recurrence occurred in 3 of 12 patients with inadequate margins and in 11 of 27 cases with indeterminate margins, only 1 of 22 patients with clearly adequate margins recurred ($p < 0.01$).

To evaluate the independent influence of different clinical and pathologic factors on local recurrence risk, a Cox multivariate analysis was performed. The following factors were entered as covariates: age (as continuous variable),

FIG. 2. Actuarial freedom from local recurrence in the treated breast for patients with macroscopically multifocal tumors, according to the retrospective review of resection margins. The numbers below the time axis indicate the patients at risk for each interval.



mode of discovery (clinical/mammographic *versus* gross pathology), number of foci (2 *versus* 3 or more), anatomic size of largest nodule (in centimeter intervals), histologic grade (1 *versus* 2 *versus* 3), EIC (absent *versus* present), resection margins (adequate *versus* indeterminate or inadequate), histologic lymph node status (negative, unknown, positive), adjuvant hormone therapy (yes, no), and adjuvant chemotherapy (yes, no). The only factor shown to have significant independent influence on the incidence of failure in the breast was the retrospective assessment of resection margins ($\chi^2 = 8.32$, $p = 0.004$). Actuarial local recurrence-free survival curves according to the adequacy of excision are presented in Figure 2.

The salient clinical and pathologic features of the 15 patients suffering local recurrence are shown in Table 2. Because the mean age was 49.8 years, there was no indication that recurrence occurred preferentially in younger patients. Mean time to local recurrence was 45.1 months, with 6 of the 15 relapses having been diagnosed after the fifth year. As is apparent in Figure 1, there was a tendency for recurrences of multifocal tumors to occur later than for single tumor foci.

Only four relapses presented as single foci in the vicinity of the primary tumors, whereas three were single recurrent tumors elsewhere in the breast, and one recurred as an apparently isolated nodule in the skin of the breast. The remaining relapses were multifocal, including diffuse in-

volvement of parenchyma and skin in three patients. This is in contrast to the 56 local recurrences in patients with unifocal cancers, 33 (59%) of which were single foci in the immediate vicinity of the original tumor bed. Follow-up after recurrence was too short to allow comment on the salvage treatment or prognosis of this small group of patients.

Discussion

Although the multicentricity of breast cancer has traditionally been used as an argument against limited surgery,^{5,6} the long-term results of breast-conserving treatment with radiotherapy suggest that the clinical relevance of multiple cancer foci documented only on pathologic examination is probably limited.^{12,18-21} However the presence of more than one macroscopically apparent tumor mass has been considered to represent a contraindication for breast preservation, even by those strongly advocating this form of treatment.⁸

The present analysis represents part of a retrospective clinicopathologic study of risk factors for local recurrence, including all evaluable stage I-II patients selected for breast-conserving surgery in a single institution during a 9-year period. Although no systematic exclusion of clinically apparent multiple tumors took place, a certain selection against such cases cannot be excluded, especially

TABLE 2. *Clinical Features and Course of the 15 Patients with Macroscopically Multiple Tumors who Developed Recurrence in the Breast*

Age (yrs.)	Mode of Diagnosis	Positive Nodes	Histo	Foci	Interval (months)	Salvage Therapy	Course (months after failure)
52	Clinical (close)	?	EIC-	2	56 single, other quad.	WE	NED 74
42	Gross path	?	EIC+	4	27 multiple, skin	Chemo	DOD 17
52	Gross path	0	EIC+	3	68 multiple, same quad.	M	DOD 8
44	Gross path	?	EIC-	2	11 single, same quad.	WE + chemo	DOD 71
61	Gross path	11	EIC-	5	24 multiple, same quad.	M + Tam	LFU 13
41	Clinical (close)	0	Inv. lobular	3	25 single, same quad.	WE	NED 72
46	Mammogr. (distant)	2	EIC-	2	34 bifocal, same quad.	WE + Tam	Recur 17 AWD 55
33	Clinical (distant)	1	EIC+	3	72 single, same quad.	WE + chemo	NED 18
75	Clinical (close)	0	EIC+	2	53 bifocal, same quad.	M	NED 23
56	Gross path	3	EIC+	4+	80 single, other quad.	WE	NED 3
68	Gross path	1	EIC-	3	72 single, same quad.	WE	NED 1
54	Gross path	0	EIC-	3	19 skin, extensive	Biopsy + chemo	Meta 3 DOD 25
45	Clinical (close)	10	EIC-	3	61 skin, localized	WE	NED 1
35	Clinical (distant)	0	EIC-	2	62 single, other quad.	WE + chemo	NED 1
43	Mammogr. (distant)	0	EIC+	2	13 diffuse, inflammatory	Chemo + Tam	AWD 36

EIC, extensive intraductal component; WE, wide excision; M, total mastectomy; Chemo, chemotherapy; Tam, tamoxifen; NED, alive with-

out active cancer; DOD, dead of cancer; AWD, alive with cancer; LFU, lost to follow-up.

given the possible technical and cosmetic difficulties associated with breast preservation in these patients and the biases of the individual surgeons involved. It is possible that some of our observations may not apply to patients with macroscopically multifocal tumors as a whole.

It is clear that macroscopic multiplicity as defined in this paper is only a facet of the spectrum of multifocality. However we have chosen to focus attention on this aspect because only those multiple foci that are apparent on clinical, mammographic, or gross pathologic examination can readily influence the pre- or intraoperative decision to proceed with conservative surgery. Using these criteria, 61 of the 586 (11%) patients in this study had macroscopically multiple tumors. In only 12 (2%) instances were the foci at a considerable distance from each other. There are very few other data in the literature pertaining to the frequency of macroscopically separate tumor masses. Fisher et al.⁷ observed two clinically and pathologically distinct lesions residing in remote quadrants in only 1 of 1000 cases reviewed. In a more recent series of patients selected for breast conservation, 10 of 697 (1.4%) patients were found to have two or more separate invasive primary lesions in the treated breast, but a clear selection bias

against such patients was in effect in the reporting institution.²²

Comparison of patient-related and tumor-related characteristics yielded very little to distinguish macroscopically multiple from unifocal tumors (Table 1). Both patient groups had a similar average age and comparable rates of estrogen-receptor positivity and lymph node involvement. Contralateral breast cancers were observed with similar frequencies and overall survival was identical. The most notable morphologic feature was a higher prevalence of EIC in patients with multiple tumors. A correlation between EIC and multiple primary lesions has also been noted by Leopold et al.²²

Our experience confirms the hypothesis that macroscopically multiple tumors have an inherently greater tendency to local failure after conservation therapy than do grossly unifocal cancers. Our attempts to identify subgroups of patients at high recurrence risk must be viewed with some degree of skepticism, given the small number of events for analysis. Patients suffering local recurrence, however, were almost exclusively confined to those in which the multiple lesions were apparent to the clinician, or in which the pathologist identified three or

more nodules on gross examination. Tumors that were close together did not tend to recur less often than those that were far apart. There appeared to be a tendency for tumors with EIC to recur more frequently, although this difference was not statistically significant. Extensive intraductal component has previously been identified as an important risk factor for local recurrence in the breast^{14,21} and has been postulated by Leopold et al.²² as being responsible for the higher recurrence rate observed in patients with multiple primary tumors. Our study neither confirms nor refutes this hypothesis.

The major weakness of this study concerns the issue of microscopic resection margins. The surgical approach in this series was based on a 'complete' wide excision of the gross lesion, with a margin of about 1 cm of macroscopically normal surrounding tissue, as judged by the operating surgeon.¹² It is likely, however, that improved local results might be achieved in these high-risk patients if intraoperative control of microscopic resection margins were to take place, with judicious use of re-excision to assure adequacy of resection.²³ The potential value of this close collaboration between surgeon and pathologist is suggested by our study of resection margins. Although it is recognized that adequacy of excision is best assessed prospectively,^{20,24} our retrospective analysis yielded interesting results, despite the substantial number of margins that were classified as indeterminate. First the surgical approach used in this series attained adequate margins significantly less often for multiple than for single tumors (Table 1). Second local failure was, with one exception, observed only in patients with inadequate or indeterminate margins. The status of resection margins proved to be the only significant predictor of local recurrence risk in the Cox multivariate analysis (Fig. 2).

As might be expected, analysis of local failures suggests that such recurrences tend to be multifocal and sometimes extensive for patients having had macroscopically multiple primary lesions (Table 2). This is in contrast with recurrences in patients with grossly unifocal cancers, which tend to be single and confined to the vicinity of the tumor bed.^{21,25} In addition recurrences in patients with multiple tumors have a tendency to occur later than in patients with single lesions (Fig. 1), raising the possibility that some of these local failures might represent previously unrecognized 'new' primary tumors in the retained breast. The possible importance of new tumor formation has been discussed in previous publications.^{21,25}

The limited scope of this study precludes firm conclusions regarding the treatment and prognosis of recurrence in these patients. However, as only 3 of the 15 local failures were treated with total mastectomy, it is likely that the extent of recurrence was underestimated in some cases. Despite the fact that two patients survived relapse free more than 6 years after wide excision of their recurrences,

conservative salvage surgery should be used with particular caution in this subgroup of patients.²⁶

It appears justified to consider patients with grossly recognizable multiple tumor foci to be at greater risk when treated with conservation therapy. This is reflected in a higher risk for local recurrence and in a tendency toward multifocal, more extensive recurrences as compared to patients with macroscopically unifocal cancers. Nonetheless retrospective review of resection margins suggests that satisfactory results can be achieved if particular attention is paid to the adequacy of excision in these high-risk patients. It is apparent that close collaboration between surgeon, pathologist, and radiation oncologist is especially important in this situation. Under these conditions, we do not consider the presence of macroscopically multiple tumor foci alone to represent a contraindication to breast-conserving surgery with radiotherapy.

Whether a conservative operation should be undertaken in the face of macroscopically multiple tumors depends, to some extent, on the degree with which the particular patient desires breast preservation. Because resection of a larger portion of the breast is sometimes necessary, it is possible that the cosmetic result may, in some cases, not meet with the expectations of the patient. It is apparent that such a judgment can best be rendered by a surgeon who has a considerable personal experience with conservative breast operations.

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Inhibition of Tumor Growth and Metastasis by Chronic Intravenous Infusion of Prostaglandin E₁

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The role of prostaglandins and their synthesis inhibitors in malignant disease is undefined. The following studies were done to determine the effects of continuous intravenous prostaglandin E₁ (PGE₁) or a prostaglandin synthesis inhibitor, indomethacin, on tumor growth and metastasis in mice bearing Lewis lung carcinoma. Male B6D2F1 mice underwent tumor implantation in the right axilla on day 0. After 10 days of tumor growth, mice underwent intravenous (IV) catheterization and were infused with either PGE₁ at 3 µg/kg/minute (PG-LOW), PGE₁ at 6 µg/kg/minute (PG-HIGH), indomethacin (INDO) at 1 µg/kg/minute, or normal saline (NS). After 10 days of infusion, tumor volume, tumor weight, and the number of metastases greater than 2 mm in diameter were significantly decreased, and tumor doubling time was significantly prolonged in the PG-HIGH group compared to NS controls. None of the other experimental groups showed differences in these parameters. A second experiment with a similar experimental design was done infusing PGE₁ at 6 µg/kg/minute and at 12 µg/kg/minute to determine the maximum dose response of IV PGE₁. Again a decrease in tumor volume, tumor weight, and metastatic rates were identified when compared to saline control, but there were no significant difference between the two doses of PGE₁.

SINCE THEIR DISCOVERY in the 1930s, prostaglandins (PG) have been found to play a role in a wide variety of physiologic processes. Aberrations in PG metabolism have also been implicated in pathologic states. The role of various PGs in vascular and renal physiology and pathology has been well characterized.^{1,2} However the role of PGs in malignant disease is less clear. For example PG synthesis inhibitors have been found to decrease tumor growth in experimental host systems.³⁻⁵ Also human malignancies, especially breast cancer, have been found to synthesize large amounts of PGs (particularly of the E series).⁶⁻¹¹ These findings suggest that the presence

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of PG is necessary for initiation and growth of tumors. In contradistinction several PGs administered *in vitro*, intralesionally, or intraperitoneally decrease tumor growth.¹²⁻¹⁶ Thus the exact role of the various PGs (and their synthesis inhibitors) in malignant disease is, as yet, undefined. The purpose of the following studies was to determine the effect of continuous intravenous PGE₁ or a PG synthesis inhibitor, indomethacin, on tumor growth and metastasis in an *in vivo* tumor-host system. A second study was done to determine if the decrease in tumor growth observed in the first experiment occurred in a dose-dependent fashion.

Materials and Methods

Description of Tumor

Lewis lung carcinoma (LLC) is an anaplastic squamous cell carcinoma that predictably metastasizes to the lungs with minimal or absent involvement of other organ systems. It was obtained from the National Cancer Institute (Bethesda, MD) and is maintained in our laboratory by serial subcutaneous transplantation in C57BL/6 mice at 10- to 14-day intervals. Subcutaneous implantation in hybrid (B6D2F1) mice results in a measurable tumor by day 8, with tumor growth logarithmic from day 10 until death at days 22 to 26. Death is attributable to pulmonary dysfunction secondary to metastases. The primary tumor may account for 25% to 30% of the tumor-host body weight at death.

Our studies on tumor growth are conducted from days 10 to 20, a period when tumor growth rate is on the logarithmic portion of the Gompertz growth curve. There is minimal hemorrhage or necrosis in the tumor, and visible surface metastatic lesions appear on the lungs.

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Experimental Design

Male B6D2F1 mice (Harlan Sprague-Dawley, Indianapolis, IN) weighing 20 to 25 g were acclimated to the laboratory for 1 week. Mice were individually housed in stainless steel cages in a temperature-controlled room with a 12-hour light/dark cycle.

Experiment 1

On day 0 mice were aseptically implanted with 1-mm³ fragments of fresh LLC tumor tissue in the subcutaneous area of the right axilla. Mice were returned to their cages and fed a casein-based diet. On day 10 tumors were sized and mice were randomized to one of four groups of mice with similar tumor volume (approximately 0.5 cc). Mice underwent inferior vena cava cannulation (as previously described)^{17,18} and were immediately connected to the infusion system. Mice were infused with one of four intravenous solutions. The normal saline (NS) group received an infusion of 0.9% NaCl. The second group, PG-LOW, received an infusion of PGE₁ in normal saline at a rate of 3 µg/kg/minute. The third group, PG-HIGH, received an infusion of PGE₁ in normal saline at 6 µg/kg/minute. The dose of PGE₁ was determined by preliminary experiments in an effort to determine if adverse effects of PGE₁ infusion would be present at various levels. Infusion of PGE₁ at the dose to maintain patency of the ductus arteriosus in human infants was used as our baseline experimental dose. Experiments in which the dosage was increased was done until 4 µg/kg/minute was reached. No adverse effects were noted at this pharmacologic level. Due to limitations in the availability of PGE₁, we chose doses at 3 and 6 µg/kg/minute. The group receiving indomethacin (INDO) received an infusion in normal saline at 1 µg/kg/minute. The indomethacin dose was chosen by doubling the dose normally given human infants to close a patent ductus arteriosus. All groups were pair fed the casein slurry diet to control for changes in tumor growth secondary to varied caloric intake. All solutions were infused at a rate of 3 mL/day.

After 10 days of infusion, mice were rapidly decapitated and exsanguinated into chilled tubes containing ethylenedinitrilo tetraacetic acid and indomethacin (10 µg per mL) to inhibit *in vitro* PG synthesis. Tumors were then sized with vernier calipers, excised, and weighed. Lungs were removed and preserved by the method of Wexler.¹⁹ Liver, kidney, spleen, stomach, and intestines were examined for evidence of abnormalities associated with PGE₁ or indomethacin infusion.

Experiment 2

The experimental design was similar to experiment 1 except only three groups were studied. Results of exper-

iment 1 showed an effect of PGE₁ infusion on the tumor-host system. To determine if a higher dose of PGE₁ infusion would lead to further changes, the following experiment was done. Mice were randomized to one of three groups with similar tumor volumes (0.5 cc). Group NS was infused with 0.9% NaCl. Group PG-6 underwent infusion of PGE₁ at 6 µg/kg/minute. Group PG-12 underwent infusion of PGE₁ at 12 µg/kg/minute. Mice were killed after 9 days of infusion and tissues were processed as described above. (Tumors from this 'pass' grew at a slightly faster rate than tumors from experiment 1.)

Analytic Techniques

Tumor volume and tumor doubling time were calculated as previously described.²⁰ Surface pulmonary nodules were enumerated blindly by two separate investigators using a dissecting microscope. Plasma was separated by centrifugation and was then frozen at -20 C. Total plasma PGE was determined by radioimmunoassay (Amersham Corp., Arlington Heights, IL).

Statistics

Statistical analysis was performed by two-way analysis of variance using Stats Plus Statistical Analysis Software (Human Systems Dynamics, Northridge, CA). Differences among means were determined by calculation of least significant difference at the 0.05 level of probability by comparing the experimental groups (PG-LOW, PG-HIGH, and INDO) to NS (controls).

Preparation of Intravenous Solutions

PGE₁ was obtained as a gift of the Upjohn Company (Kalamazoo, MI). PGE₁ was stored in 100% ethanol at -12 C at a concentration of 10 mg/mL. The calculated amount of PGE₁ stock solution was then aseptically added to the infusion bag of normal saline, slowly, to avoid precipitation. The infusion bags were sonicated for 3 to 5 minutes and then connected to the infusion system. Solutions were changed daily.

Indomethacin was obtained commercially from Merck, Sharp, and Dohme (West Point, PA) and stored as a powder at room temperature. It was aseptically constituted daily in 0.9% NaCl as a stock solution and then added to the infusion bags.

An appropriate amount of 100% ethanol was added to each infusion bag because the diluent for PGE₁ was ethanol. This was done so that all groups received an equivalent amount of ethanol (Approximately 10 mL ethanol per liter of normal saline).

TABLE 1. *Experiment 1: Tumor and Metastasis Growth Parameters*

Group	Increase in Tumor Volume (cm ³)	Final Tumor Weight (g)	Tumor Doubling Time (days)	No. of Lung Metastasis	No. of Metastasis >2 mm diameter	Total Plasma PGE (μg/mL)
NS (n = 9)	4.1 ± 0.5	7.0 ± 0.5	3.2 ± 0.1	34 ± 7	1.9 ± 0.6	10.4 ± 0.4
PG-LOW (n = 8)	3.4 ± 0.3	6.2 ± 0.6	3.3 ± 0.2	38 ± 1	1.8 ± 1.1	58.3 ± 6.0*
PG-HIGH (n = 7)	2.4 ± 0.3*	4.7 ± 0.4*	4.2 ± 0.3*	18 ± 4	0.1 ± 0.1*	68.5 ± 11.3*
INDO (n = 10)	3.9 ± 0.3	7.2 ± 0.6	3.5 ± 0.2	27 ± 7	0.6 ± 0.2	6.8 ± 1.2*

Values are mean ± SEM: * indicates significant difference ($p < 0.05$) by ANOVA vs. NS; (n). NS, normal saline; PG-LOW, PGE₁ of 3 μg/kg/

min; PG-HIGH, PGE₁ at 6 μg/kg/min; INDO, indomethacin at 1 μg/kg/min. Flow rates = 3 cc/day.

Results

Experiment 1

Food consumption, mortality rates, and carcass weights were similar among experimental groups. Mice gained an average 2.3 g body weight. Plasma PGE₁ was significantly increased 657% ± 13% (mean ± SEM) in the PG-HIGH group and 560% ± 60% in the PG-LOW group, indicating that pharmacologic levels were achieved in the blood (Table 1). Plasma PGE was significantly decreased by 34% ± 11% in the INDO group, verifying inhibition of PG synthesis. Liver weight was significantly lower in the PG-HIGH group. Kidney and spleen weights and gastrointestinal length were not different among groups. Gross inspection of the stomach revealed no evidence of ulceration or gastritis in any of the experimental groups.

Intravenous infusion of PGE₁ at 6 μg/kg/minute significantly inhibited primary tumor volume by 38% ($p = 0.013$) and primary tumor weight by 33% ($p = 0.004$). Tumor doubling time was prolonged by 31% ($p = 0.006$) in the PG-HIGH group. The number of lung metastasis was decreased by 47% in the PG-HIGH group but this did not reach statistical significance at the 5% level ($p = 0.07$). However the number of lung metastasis larger than 2 mm in diameter was significantly decreased by 95% in the PG-HIGH group.

Intravenous infusion of PGE₁ at 3 μg/kg/minute exhibited a dose-dependent trend toward a decrease in tumor volume and weight ($p = 0.1403$ and $p = 0.0753$, respectively) but did not reach statistical significance. Tumor doubling time, total number of lung metastasis, and the number of metastasis larger than 2 mm in diameter were not significantly different from normal saline controls.

Intravenous infusion of indomethacin did not significantly affect any of the tumor growth parameters studied.

Experiment 2

Food consumption, mortality rates, and carcass weights were similar among experimental groups. Mice gained an average of 1.4 g. Plasma PGE significantly increased 717% ± 38% (mean ± SEM) in the PG-12 group and 542% ± 66% in the PG-6 group, indicating that pharmacologic levels were achieved in the blood (Table 2).

Intravenous infusion of PGE₁ at 12 μg/kg/minute inhibited primary tumor volume by 47% ($p = 0.0142$) and primary tumor weight by 27% ($p = 0.024$). Tumor doubling time was prolonged by 41%. The number of lung metastasis decreased by 45%.

Intravenous infusion of PGE₁ at 6 μg/kg/minute inhibited primary tumor volume and weight by 41% ($p = 0.0282$) and 21% ($p = 0.044$), respectively. Tumor doubling time was prolonged by 31%. The number of pulmonary metastasis was decreased by 35%. These changes were consistent with those observed in experiment 1 using the same dosage.

There was no significant difference in tumor weight, volume, doubling time, or number of lung metastasis between the PG-6 and the PG-12 groups.

Discussion

The ubiquitous nature of the prostaglandins makes them extremely difficult to characterize. Not only do the various prostaglandins behave differently but the same prostaglandin may exert a wide spectrum of responses, depending on the state of the host at the time of study.

TABLE 2. *Experiment 2: Tumor and Metastatic Growth Parameters*

Group	Increase in Tumor Volume (cm ³)	Final Tumor Weight (g)	Tumor Doubling Time (days)	No. of Lung Metastasis	Total Plasma PGE (μg/mL)
NS (n = 9)	3.6 ± 0.6	7.6 ± 0.8	3.2 ± 0.3	31 ± 4	10.2 ± 0.2
PG-6 (n = 6)	2.1 ± 0.3*	5.9 ± 0.3*	4.2 ± 0.3*	20 ± 4*	60.4 ± 6.7*
PG-12 (n = 9)	1.9 ± 0.2*	5.5 ± 0.3*	4.5 ± 0.4*	17 ± 3*	73.1 ± 3.9*

Values are mean ± S.E.M.: * indicates significant difference ($p < 0.05$)

by ANOVA vs. NS; (n). NS, normal saline; PG-6, PGE₁ at 6 μg/kg/min; PG-12, PGE₁ at 12 μg/kg/min. Flow rates, 3 cc/day.

Thus studies examining the role of prostaglandins in malignant states requires stringent attention to all aspects of the study, including mode of delivery of the experimental compound, selection of tumor-host system, and selection of study parameters.

Because prostaglandins are paracrine hormones, their *in vivo* half-life is extremely short (0.5 to 3.0 minutes). Thus the route of delivery of prostaglandins is crucial. In 1983 we developed a model for chronic intravenous infusion in mice.^{17,18} We used this model in these studies in an attempt to sustain pharmacologic levels of circulating prostaglandin E₁. Intramuscular, subcutaneous, or intraperitoneal injections of prostaglandins may not allow for chronic, steady-state levels. Thus uptake and distribution of these compounds may be variable. In the present study, we confirmed the appearance of pharmacologic levels of prostaglandin E₁ in the blood by showing that IV infusion of PGE₁ caused a five- and sixfold increase in the plasma of the stable bicyclic metabolite 13, 14-dihydro-15-Keto-prostaglandin E after alkalization *in vitro*. Delivery of prostaglandin was directly into the inferior vena cava and thus traversed the lungs before systemic circulation. Prostaglandin E is metabolized by the lung and approximately 90% is converted to an inactive compound on first pass. Thus the amount reaching the systemic circulation was probably only a fraction of the infused dose.

Experiment 1 was done to further elucidate the role of PGE₁ in malignant growth and spread. We also administered a prostaglandin synthesis inhibitor to determine if intravenous infusion of these compounds would have contrasting effects on tumor growth. It was found that high levels of prostaglandin E₁ (6 $\mu\text{g/kg/minute}$) decreased tumor growth and metastatic growth, but indomethacin did not cause any alterations in these tumor growth parameters.

Experiment 2 answered several additional questions. First it confirmed our findings of experiment 1, *i.e.*, that IV infusion of PGE₁ at 6 $\mu\text{g/kg/minute}$ caused a decrease in tumor growth. Second we found that increasing the dose of PGE₁ to 12 $\mu\text{g/kg/minute}$ did not lead to a further decrease in tumor growth. Thus the limit of effectiveness of PGE₁ in this tumor host system was obtained at 6 $\mu\text{g/kg/minute}$. Third in experiment 1 we found a trend toward a decrease in metastasis in the group infused with prostaglandin E₁ at 6 $\mu\text{g/kg/minute}$, yet statistical significance was not attained. In experiment 2 a statistically significant ($p < 0.05$) decrease in the total number of metastases was obtained at the doses of PGE₁ used. The discrepancy between the two experiments is probably a reflection of the larger number of mice in experiment 2. Thus the failure to reach statistical significance in experiment 1 was probably a type 2 statistical error.

Side effects from intravenous infusion of prostaglandin and indomethacin were not obvious. Prostaglandin E₁ is a vasodilator and also a stimulator of gastrointestinal motility.²¹ Prostaglandin synthesis inhibitors are known to be caustic to the gastrointestinal tract. However, in the present study, we observed that feeding habits, grooming patterns, urine output, stool consistency, mortality rates, and other indicators of normal behavior were not affected by PGE₁ or indomethacin infusions.

The type of tumor host system is important in planning experiments and studying the role of prostaglandin in malignant diseases. Most human tumors synthesize prostaglandin E as their primary eicosanoid.^{6,7,22} Lewis lung carcinoma thus serves as a representative rodent tumor model of a PGE-producing tumor line because PGE is also its primary arachidonic acid derivative. Other tumor-host systems synthesize prostaglandins, but the primary eicosanoid metabolite varies with the tumor-host system. For example the primary biproduct of eicosanoid synthesis of the B-16 melanoma is prostaglandin D.²³

Plescia²⁴ found prostaglandin E to be immunosuppressive in a murine tumor-host system. Since then prostaglandins have been found to be strong modulators of the immune system.²⁵⁻²⁷ Furthermore immunosuppression in cancer patients has been reversed (*in vivo* and *in vitro* studies) by prostaglandin synthesis inhibitors.²⁶⁻²⁸ The role of PGE in modulating the immune system in the present study was not determined. Immune studies would not fully explain our findings of decreased tumor growth with prostaglandin E infusion. Variation in tumor growth among groups may be modulated by the growing tumor, prostaglandin E₁ infusion, or both. It would not be possible to discern the immunomodulation properties of the tumor and/or prostaglandin E₁ in our experimental model. Furthermore because Lewis lung carcinoma is carried in our laboratory by serial transplantation *in vivo*, immunogenic tumor cells would be selected out after many transplantations. However we cannot conclusively rule out that immunologic factors were not responsible for our observations. In fact, despite early reports of the immunosuppressive effects of prostaglandins in the tumor-bearing host, prostaglandins have been found to be immunostimulatory in tumor-bearing rodents.²² Thus prostaglandin metabolism is altered by other host factors *in vivo*.

Many investigators have shown that inhibition of prostaglandin synthesis can decrease tumor growth or even cause tumor regression in experimental models.³⁻⁵ Most of this work has been done with nonsteroidal anti-inflammatory agents such as indomethacin or aspirin. Recent work with omega-3 fatty acids also has shown that these lipids decrease tumor growth, mediated possibly through a decrease in prostaglandin synthesis. In contradistinction

in vitro studies have shown that cultured tumor cells treated with indomethacin increase cell proliferation and decrease differentiation.²³ Still others have found that oral administration of a prostaglandin synthesis inhibitor increases the risk of carcinogen-induced GI neoplasms.³⁰ Our study examined the effects of intravenous infusion of indomethacin on *in vivo* tumor growth. We found no effect of indomethacin on tumor growth or metastasis, despite a significant reduction of plasma PGE concentration. Our study, along with others, strongly suggests that the effects of prostaglandin synthesis inhibitor on tumor growth are dependent on the route of delivery, as well as the tumor host system. To our knowledge there is no study suggesting that chronic IV infusion of indomethacin decreases tumor growth.

The exact mechanism by which PGE decreases cell proliferation in tumor growth is not known. Initially it was thought to be mediated through cyclic AMP. Recently Jaffe et al.²¹ outlined several convincing arguments against this theory and proposed that 'prostaglandins may mediate the antiproliferative activity of the cyclic nucleotide rather than the opposite end.' Others have shown that several of the prostaglandins inhibit DNA synthesis. *In vitro* studies by Ono et al.³¹ have shown that this occurs by decreases in DNA polymerase activities that are accompanied by an inhibition of tumor cell growth. Another mechanism for decreased tumor cell proliferation has been suggested by Neu et al.,³² who observed that prostaglandins may decrease protein synthesis. One or more of these mechanisms may account for our observations. Recently research efforts have focused on immunomodulation of tumor-bearing hosts by lymphokines. There is evidence that various immunomodulators, such as the prostaglandins and other lymphokines, modulate each other in addition to modulating cellular differentiation and function. In *in vitro* studies, PGE has been found to decrease lymphokine production, whereas interleukin-1 and interleukin-2 increase prostaglandin production in monocytes.³³⁻³⁵ Further work may establish the complex interrelationships between the prostaglandins and other cytokines. It is difficult to base findings from our studies on present knowledge of these interrelationships.

The effect of prostaglandins on tumor metastasis appears to occur at the level of the primary neoplasm. Powles et al.,³⁶ have shown that prostaglandin synthesis inhibitors decreases the development of bone metastasis in rats injected with tumor cells intravenously. This is consistent with other work from our laboratory showing that IV administration of prostaglandin E₁ enhances growth and rates of artificial metastases. Similarly prostaglandins have been shown to augment tumor cell migration as an *in vitro* model for metastases.³⁷ The effect of prostaglandin E₁ on the metastatic cascade is not known. PGE₁ is a

potent pulmonary vasodilator and, thus, may decrease trapping of cells in the pulmonary vasculature, thereby preventing formation of metastases. PGE₁ also has anti-aggregatory activities that are similar to, but less than, those of prostacyclin (PGI₂). Experimentally anti-coagulants have been found to decrease metastatic rates and this feature may account for our observations.^{38,39}

The present studies examine the effects of prostaglandin E₁ in the middle to latter stages of tumor growth and metastasis. The role of PGE₁ in tumor initiation and growth is presently being investigated. These studies, as well as others, help to elucidate the role of PGE₁ in malignant diseases. In addition these studies suggest that PGE₁ may potentially serve as a chemotherapeutic agent or a component of chemotherapeutic regimens. PGE₁ has been found to be cytoprotective to the gastrointestinal tract⁴⁰ and, thus, may serve to limit the severity of chemotherapeutically induced gastrointestinal toxicity. Recently Gaskins⁴¹ found that intraportal PGE₁ limits the toxicity of hepatic infusions of FUDR. The effects of administration of PGE₁ in conjunction with traditional chemotherapeutic agents have yet to be determined.

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Management of Primary and Recurrent Soft-tissue Sarcoma of the Retroperitoneum

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From 1982 to 1987, 114 patients underwent operation at Memorial Sloan-Kettering Cancer Center for soft-tissue sarcoma of the retroperitoneum. A retrospective analysis of these patients defines the biologic behavior, surgical management of primary and recurrent disease, predictive factors for outcome, and impact of multimodality therapy. Complete resection was possible in 65% of primary retroperitoneal sarcomas and strongly predicts outcome ($p < 0.001$). The rate of complete resection was not altered by histologic type, size, or grade of tumor. These patients had a median survival of 60 months compared to 24 months for those undergoing partial resection and 12 months for those with unresectable tumors. Forty-nine per cent of completely resected patients have had local recurrence. This is the site of first recurrence in 75% of patients. These patients undergo reoperation when feasible. Complete resection of recurrent disease was performed in 39 of 88 (44%) operations, with a 41-month median survival time after reoperation. Tumor grade was a significant predictor of outcome ($p < 0.001$). High-grade tumors ($n = 65$) were associated with a 20-month median survival time compared to 80 months for low-grade tumors ($n = 49$). Gender, histologic type, size, previous biopsy, and partial resection *versus* unresectable tumors did not predict outcome by univariate analysis. Adjuvant radiation therapy and chemotherapy could not be shown to have significant impact on survival. Concerted attempt at complete resection of both primary and recurrent retroperitoneal soft-tissue sarcoma is indicated.

IN 1954 PACK AND Tabah¹ first reported the Memorial Sloan-Kettering Cancer Center (MSKCC) experience with retroperitoneal sarcoma from 1926 to 1951. They defined the clinicopathologic features and emphasized aggressive surgical management. These principles are unchanged. Current chemotherapy for retroperitoneal sarcomas is ineffective and toxicity of radiotherapy limits

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the use of adequate, potentially therapeutic doses. The anatomic location and invasiveness of retroperitoneal sarcomas often prevents resection with adequate margins. When the principles of sarcoma management learned from the treatment of extremity soft-tissue sarcoma cannot be applied, outcome is adversely affected.

A recent series of patients with retroperitoneal sarcoma is reviewed to focus on issues of biologic behavior, surgical management of primary and recurrent neoplasms, factors predictive of outcome, and impact of multimodality therapy.

Materials and Methods

Adult patients (more than 16 years old) admitted to MSKCC from July 1982 to July 1987 with the diagnosis of retroperitoneal sarcoma were identified in the Department of Surgery Prospective Sarcoma Database. Patients who underwent an operation at MSKCC for primary or recurrent retroperitoneal sarcoma are the basis for this study.

All pathologic slides were reviewed by one pathologist (SIH) to confirm histologic diagnosis and grade. Survival was calculated according to the method of Kaplan and Meier.² The log-rank test was used to compare differences in survival distributions observed in subsets of patients.³ All survival curves include operative deaths. All survival endpoints are based on death from disease, although only one patient died of other causes. Survival duration was measured from time of initial operation at MSKCC, which accounts for the prolonged survival seen in some patients admitted for a second or subsequent operation during the period 1982 to 1987.

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Results

From July 1982 to July 1987, 995 adult patients were admitted to MSKCC with the diagnosis of soft-tissue sarcoma. Of these, 146 patients (15%) had a retroperitoneal neoplasm. One hundred fourteen patients underwent an operation at MSKCC for the primary or recurrent tumor and form the basis of this review.

There were 67 male and 47 female patients. The median age at diagnosis was 57 years (range, 17 to 82 years). Sixty-three (55%) patients were treated for primary disease at MSKCC. Thirty-three patients presented to MSKCC with a first recurrence, 12 with a second recurrence, and six with a third recurrence (Table 1).

Liposarcoma (50%) and leiomyosarcoma (29%) comprised the majority of the histologic types (Table 2). Sarcomas are graded as either low or high at MSKCC.⁴ The histologic grade of sarcoma was low in 43% and high in 57% (Table 2). Size of diameter of the primary tumor was 5 to 10 cm in seven patients, 10 to 20 cm in 46, and more than 20 cm in 61 patients. No tumor was less than 5 cm in diameter at presentation. By the AJCC staging system,⁵ there were 49 G1T2N0M0 (stage I), 61 G3T2N0M0 (stage III), 1 G3T2N1M0 (stage III), and 3 G3T2N0M1 (stage IV). By the MSKCC staging system, all retroperitoneal sarcomas in this series had at least two of the three unfavorable signs as all were deep and measured more than 5 cm.

Patients generally presented with an abdominal mass (78%) and pain (50%). Neurologic symptoms, primarily sensory, were described in 27% of patients. Weight loss of more than 5 kg was noted in 7% of patients.

One hundred fourteen patients underwent 151 operations at MSKCC. Major morbidity (*e.g.*, pulmonary embolus, myocardial infarction, sepsis) occurred after 14% of the operations and minor morbidity (*e.g.*, wound infection, atelectasis) occurred in 9%. The 30-day operative mortality rate was 4% (6 of 151 operations); all but one postoperative death occurred after operation for unresectable recurrent disease. Cause of death included sepsis, myocardial infarction, and multiple-organ failure and no deaths were due to progression of disease.

Complete resection was defined as resection of all gross disease. Positive microscopic pathologic margins were

TABLE 2. Distribution of Adult Retroperitoneal Sarcomas by Histologic Type and Grade

Histology	Low Grade	High Grade	Total (%)
Liposarcoma	34	23	57 (50%)
Leiomyosarcoma	6	27	33 (29%)
Hemangiosarcoma	3	4	7 (6%)
Fibrosarcoma	4	2	6 (5%)
Malignant fibrous histiocytoma	0	5	5 (4%)
Malig. peripheral nerve tumor	1	3	4 (4%)
Alveolar soft part sarcoma	1	0	1 (1%)
Embryonal rhabdomyosarcoma	0	1	1 (1%)

noted in 12 of 41 complete resections for primary neoplasms. This did not predict early recurrence or death from disease. Complete resection at first MSKCC operation was performed in 59% of cases and ranged from 65% for primary neoplasms to 44% for recurrent disease (Table 1). The rate of complete resection was not altered by histologic type, size, or grade of tumor (low, 61% complete resection; high, 57% complete resection). Resection of adjacent organs was required in 83% of patients undergoing complete resection. Fifty-three per cent had one organ resected and 30% had more than one organ resected. Resected adjacent organs included kidney (46%), colon (24%), and pancreas (15%) (Table 3). Pathologic involvement of the kidney was noted in 2 of 30 nephrectomies. Major vascular resection, vena cava, common iliac artery or vein, was performed in 7 of 67 completely resected patients. Eighteen of thirty-three (54%) initially unresectable patients referred to MSKCC had complete resection of their tumors.

Partial resection designated operations in which more than 80% of the tumor was resected but gross residual disease was present. Twenty-five patients had partial resection at MSKCC for primary or recurrent tumor. The histologic types were liposarcoma (14), leiomyosarcoma (6), and other sarcomas (5). There were 17 low-grade sarcomas and 8 high-grade sarcomas. Low-grade liposarcoma accounted for 11 of 25 partial resections. Six patients have had more than one partial resection. Adjacent organs were rarely resected in this group.

Patients found to have unresectable disease generally had a biopsy only, although some had resection of bulky tumor to relieve bowel obstruction. Forty-six patients were

TABLE 1. Retroperitoneal Soft-tissue Sarcoma Resectability at First MSKCC Operation

Status at First Presentation	Complete Resection		Partial Resection		Unresectable	
	n	%	n	%	n	%
Primary sarcoma, n = 63	41	65%	9	14%	13	21%
First recurrence, n = 33	18	55%	5	15%	10	30%
≥ second recurrence, n = 18	8	44%	3	17%	7	39%
All patients, n = 114	67	59%	17	15%	30	26%

TABLE 3. Retroperitoneal Soft-tissue Sarcoma: Resection of Adjacent Organs at Primary Operation

Organ Resected	% of Patients
Kidney	46
Colon	24
Pancreas	15
Major vascular	10
Spleen	10

TABLE 4. Retroperitoneal Sarcomas: Basis for Unresectability (n = 46)

Basis	% of Patients
Vascular involvement	43
Peritoneal implants	28
Distant metastasis	19
Extensive disease	17
Root of mesentery involvement	8
Spinal cord involvement	6

unresectable at time of primary (13 of 63 [21%] patients) or recurrent (33 of 88 [38%] patients) operation at MSKCC. Forty-three per cent had extensive vascular involvement of the aorta or other vessels, *e.g.*, vena cava or iliac vessels, as the indication for unresectability. Peritoneal implants indicated unresectability in 28% and distant metastases in 19% (Table 4). Sixty-three per cent of these patients had high-grade tumors and 37% were low grade. Forty per cent of these sarcomas measured 10 to 20 cm and 60% measured more than 20 cm in diameter.

Univariate analysis of prognostic factors determining survival are shown in Table 5. Grade (Fig. 1) and resectability (Fig. 2) significantly affected survival ($p < 0.001$). Median survival time for the 49 patients with low-grade sarcomas was 80 months compared to 20 months for 65 patients with high-grade sarcomas. Complete resection was associated with 64-month median survival compared

TABLE 5. Retroperitoneal Soft-tissue Sarcoma: Distribution of Distant Metastases by Histologic Type

Histology	No. of Patients	No. of Pulmonary Mets.	No. of Hepatic Mets.
Liposarcoma	57	4	0
Leiomyosarcoma	33	3	7
Other sarcoma	24	0	3
Total	114	7 (6%)	10 (9%)

Mets., metastases.

to 24 and 12 months for partially resected and unresected patients, respectively. Age less than 53 years was a significant factor positively affecting survival time ($p < 0.05$). Gender, histologic type, size, previous biopsy, adjuvant radiotherapy, adjuvant chemotherapy, and partial *versus* unresectable operation were not shown to be statistically significant prognostic factors for survival time.

At 31 months median follow-up, 33 of 67 (49%) patients who underwent complete resection at MSKCC for primary or recurrent disease have recurred. Twenty of thirty-seven (54%) completely resected high-grade sarcomas have recurred compared to 13 of 30 (44%) low-grade sarcomas. The median time to recurrence, for those who recurred, was 15 months for high-grade sarcomas and 42 months for low-grade sarcomas (range, 2 to 144 months; Fig. 3).

Local recurrence was the predominant site of first recurrence (Table 6). Local recurrence was the only site of

Retroperitoneal Soft Tissue Sarcoma

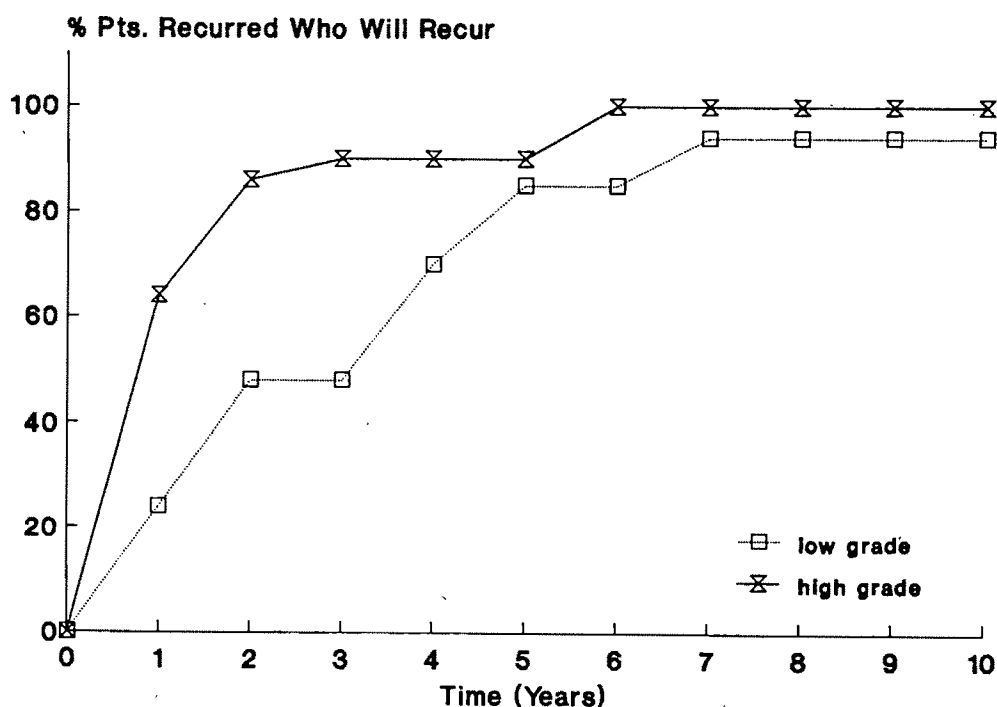


FIG. 1. Proportion of alive patients is plotted against time from first MSKCC operation according to the method of Kaplan and Meier for patients with high-grade or low-grade soft-tissue sarcoma of the retroperitoneum.

SURVIVAL OF 114 PATIENTS WITH RETROPERITONEAL SARCOMA BY RESECTABILITY

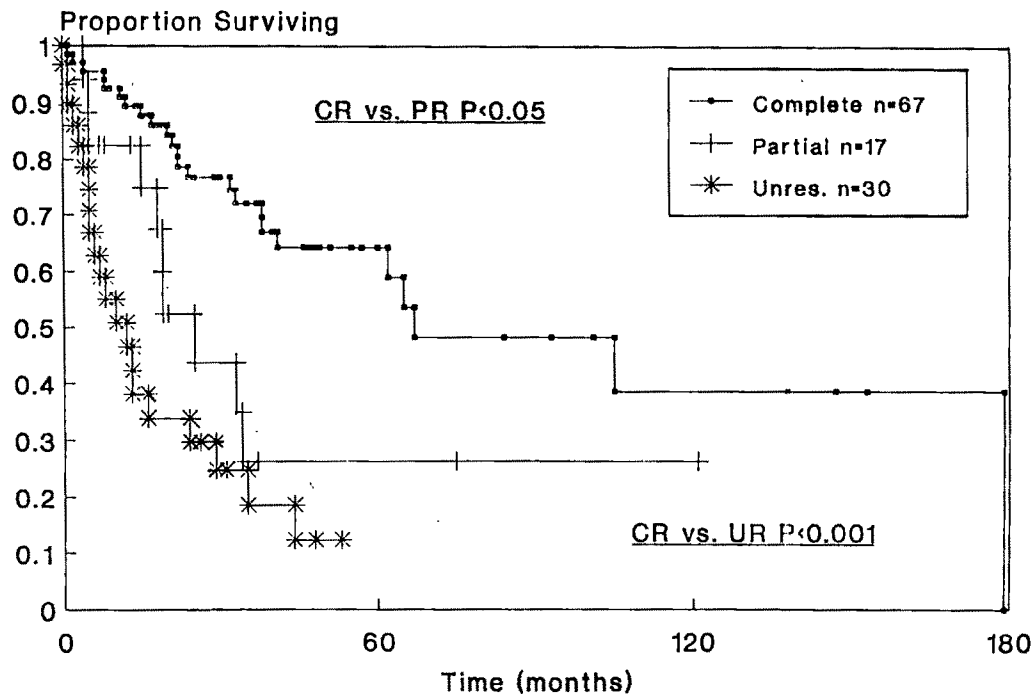


FIG. 2. Proportion of alive patients is plotted against time from first MSKCC operation according to the method of Kaplan and Meier for patients undergoing complete resection, partial resection, or unresectable operations for soft-tissue sarcoma of the retroperitoneum.

SURVIVAL OF 114 PATIENTS WITH RETROPERITONEAL SARCOMA BY GRADE

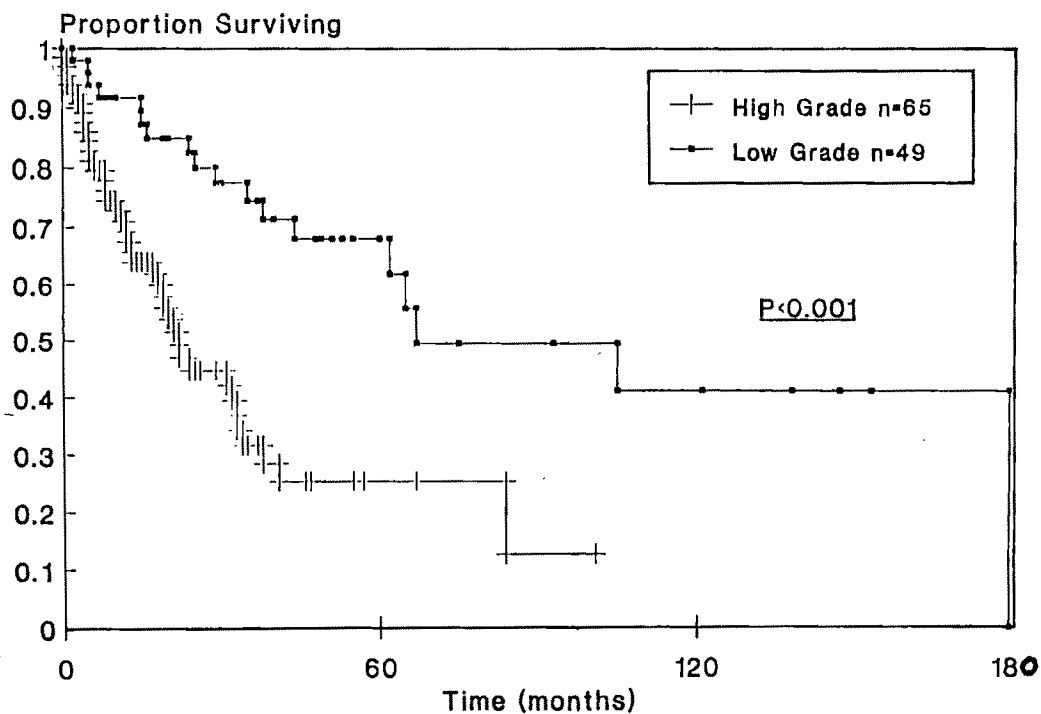


FIG. 3. Cumulative recurrence is plotted against time for patients who recurred after complete resection of high-grade or low-grade soft-tissue sarcoma of the retroperitoneum.

TABLE 6. *Retroperitoneal Soft-tissue Sarcoma: Site of First Recurrence After Complete Resection*

Site of Recurrence	Primary Disease (n = 41)	Recurrent Disease (n = 39)
Local only	12	22
Local and liver	3	1
Liver only	1	0
Lung only	2	1
Total	18 (44%)	24 (62%)

first recurrence in 75% of patients treated for primary retroperitoneal sarcoma. After complete resection of recurrent disease, 90% of recurrences were again local. Median survival from time of local recurrence was 24 months (range, 9 to 167 months). Median survival after recurrence was 15 months for high-grade sarcomas and 30 months for low-grade sarcomas.

Synchronous metastases were observed in three patients, two with hepatic metastases and one with lung metastases. Only 1 of 114 (0.8%) patients developed regional nodal metastases. Metachronous distant metastases developed in an additional 14 patients. The lung was a site of metastases in 7 of 114 (6%) patients and liver in 10 of 114 (9%) patients (Table 7). Eight of thirty-three leiomyosarcomas and 0 of 57 liposarcomas metastasized to the liver. Fourteen of seventeen patients with distant metastasis had high-grade sarcomas. Two patients with pulmonary metastases were resected, with one having no evidence of disease (NED) at 2 months follow-up and one dead of disease (DOD) 11 months after thoracotomy. One patient has had two hepatic wedge resections for metastatic leiomyosarcoma and shows no evidence of disease at 18 months follow-up. Median survival from time of distant metastases was 14 months (range, 4 to 48 months).

In the absence of clear signs of unresectability, patients with local or distant recurrence were surgically explored.

TABLE 7. *Retroperitoneal Sarcomas: Prognostic Factors for Survival by Univariate Analysis*

Factor	p value
Grade (high vs. low)	<0.001
Resectability	
Complete resection vs. unresectable	<0.001
Complete resection vs. partial resection	<0.05
Partial resection vs. unresectable	NS
Age (<53 years vs. >53 years)	<0.05
Sex (male vs. female)	NS
Histology	
Liposarcoma vs. leiomyosarcoma	NS
Liposarcoma vs. all others	NS
Leiomyosarcoma vs. all others	NS
Size (>20 cm vs. 10–20 cm)	NS
Previous biopsy	NS
Adjuvant radiation therapy	NS
Adjuvant chemotherapy	NS

Sixteen of 63 patients primarily treated at MSKCC have recurred. Fourteen (88%) were considered operable and five (31%) had complete resection for recurrent disease. Fifty-one patients referred to MSKCC with recurrent retroperitoneal sarcoma underwent reoperation and 26 (51%) had complete resection. Histologic distribution was liposarcoma (35; 54%), leiomyosarcoma (16; 25%), and other sarcomas (14; 21%). Thirty-seven (57%) patients had high-grade sarcomas and 28 (43%) had low-grade tumors. This distribution is identical to that seen in patients with primary disease. The median time to recurrent operation was 19 months from diagnosis (range, 1 to 180 months).

There were 88 operations for recurrent disease. Sixteen per cent major morbidity and 8% minor morbidity was observed. There were five 30-day operative deaths (6%). Each of these patients had unresectable disease and in three of five patients the operation was for palliative intent.

Recurrent sarcomas of the retroperitoneum were completely resected in 39 of 88 (44%) operations (Table 8). Complete resection was possible in 49%, 42%, and 33% of first, second, and third recurrences, respectively. Resection of an adjacent organ was required in 20 of 39 (51%) completely resected recurrences. The most commonly resected organs were the colon (10) and small intestine (7). Completely resected patients had a 48-month median survival time compared to 21 and 15 months for partial and unresectable patients, respectively (Fig. 4). Fourteen of sixty-five patients with operable recurrences (22%) showed no evidence of disease at median follow-up of 38 months (range, 9 to 167 months). Nine of these patients had low-grade tumors.

Adjuvant therapy was given to 18 of 41 (44%) patients after complete resection of primary sarcomas. Ten received an adriamycin-containing chemotherapy regimen and 11 received radiation therapy (~4500 rad). No differences in survival could be detected in these nonrandomized groups.

Unresectable and metastatic disease were treated with adriamycin as a single agent or in combination, or by phase I drugs. Few partial responses and no complete responses were observed. Radiation therapy was used in 22% of patients with persistent disease, with no significant responses documented. Brachytherapy was used in 7 of

TABLE 8. *Retroperitoneal Soft-tissue Sarcoma Operations for Recurrent Sarcoma*

No. of Recurrences	Complete Resections		Partial Resections		Unresectable	
	n	%	n	%	n	%
Recurrence 1 (n = 47)	23	49	7	15	17	36
Recurrence 2 (n = 26)	11	42	6	23	9	35
Recurrence 3 (n = 15)	5	33	3	20	7	47
Total (n = 88)	39	44	16	18	33	38

SURVIVAL OF 65 PATIENTS WITH RECURRENT RETROPERITONEAL SARCOMA
BY RESECTABILITY OF RECURRENCE

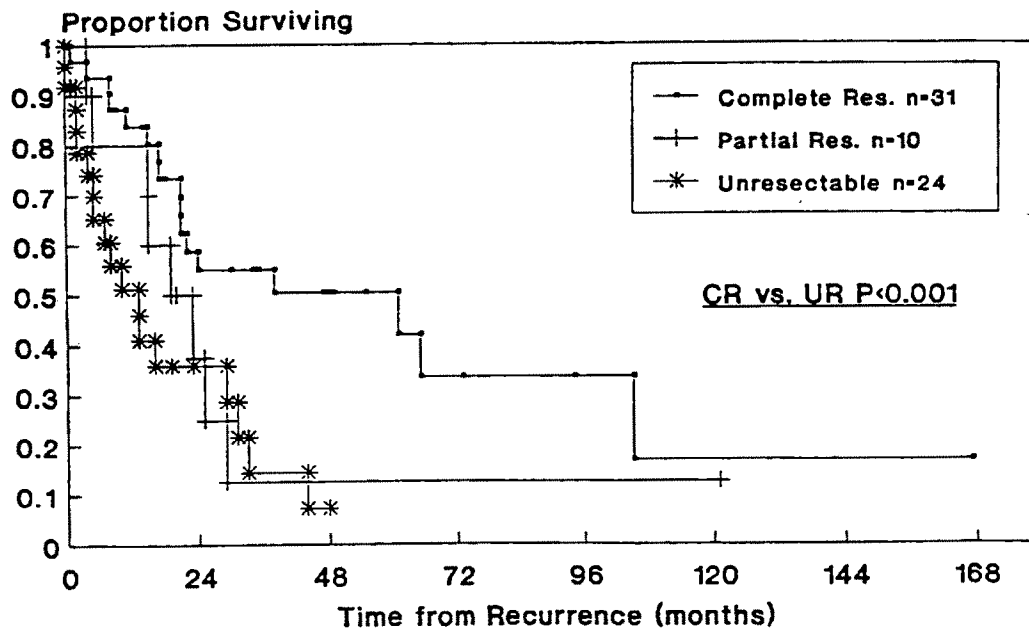


FIG. 4. Proportion of alive patients is plotted against time from first recurrence operation at MSKCC according to the method of Kaplan and Meier for patients undergoing complete resection, partial resection, or unresectable operations for recurrent soft-tissue sarcoma of the retroperitoneum.

25 partial resections. One patient has no evidence of disease at 141 months. The others had local progression of disease and death from 12 to 22 months later.

Discussion

The retroperitoneum is the site of 146 of 995 (15%) soft-tissue sarcomas treated at MSKCC from 1982 to 1987. Pooled data from several series^{1,6-9} shows that 85% of the tumors arising from the retroperitoneum are malignant and 35% are sarcomas. Histologic type is predominantly liposarcoma (50%) and leiomyosarcoma (29%). Previous reviews have described specific behavior of retroperitoneal liposarcoma,^{10,11} leiomyosarcoma,^{12,13} malignant fibrous histiocytoma,¹⁴ and synovial cell sarcoma.¹⁵ Histologic type alone does not predict outcome, although patterns of metastasis vary by histology. The pathologic grade of the tumor is high in 57% of patients with retroperitoneal sarcoma and low in 43%. This is the strongest predictor of survival and is the dominant basis for the AJC staging system. Lymph node metastases are rare (0.8%) and do not play a role in the surgical management of these patients.

Because surgical resection is essential, careful preoperative evaluation is necessary, but a liberal exploration policy is used. Preoperative evaluation should include computed tomography (CT)¹⁶ or magnetic resonance imaging (MRI).¹⁷ Angiography is uncommonly used¹⁸ and

MRI often obviates the need for venography. Bilateral renal function must be ascertained because nephrectomy is often performed (37%). Bowel preparation is indicated because 33% undergo bowel resection. Synchronous metastases were seen in 7% of patients, with the lung (41%) and liver (59%) the most common ultimate site of metastases. Thus metastatic survey includes chest x-ray and CT/MRI of the liver.

Preoperative needle biopsy is not practiced.⁴ Intraoperative open biopsy is reserved for unresectable tumors or tumors that must be distinguished from lymphoma. A transperitoneal approach is always used. A wide *en bloc* resection of the tumor with a margin of normal tissues is indicated. This is only possible with the frequent resection of adjacent organs (83%). Resection of kidney, colon, pancreas, spleen, and major vascular structures should be anticipated and is not an indication of unresectability.

With this approach 65% of patients with primary retroperitoneal sarcoma were completely resected. This compares to rates of 38% to 70% in previous surgical series^{9,19-23} (Table 9). The median survival time after complete resection was 60 months.

Partial resection was performed in 16% of the operations for primary or recurrent retroperitoneal sarcoma. This was designed for palliation to relieve obstruction or reduce the size of an intra-abdominal mass. Nephrectomy is not performed when only incomplete removal of the

TABLE 9. *Retroperitoneal Soft-tissue Sarcoma: Survival After Complete Resection of Primary Sarcoma*

Series	Years Studied	No. of Patients	5-year Survival (%)
Cody ¹⁹ (MSKCC)	1951–1974	47	40
Glenn ²² (N.C.I.)	1975–1981	37	23
Kinsella ²³ (N.C.I.)	1980–1985	35	40
Braasch ⁹ (Lahey)	1930–1960	15	40
Wist ²⁵ (Norway)	1978–1982	13	50
Karakousis ²⁰ (Roswell Park)	1957–1980	27	64
McGrath ²¹ (M.C.V.)	1964–1982	18	70
Current series (MSKCC)	1982–1987	41	74
Total		233	50

tumor is possible. No improvement in survival could be statistically shown for this therapy *versus* biopsy only. Extensive retroperitoneal involvement characterizes many low-grade liposarcomas prohibiting complete resection. Some of these patients have had prolonged palliation and survival (range, 2 to 160 months) with partial resection.

Forty per cent of patients were unresectable at primary or recurrent operation at MSKCC. Vascular invasion most frequently limits resectability. Unsuspected hepatic metastases, extensive disease, involvement of the root of the mesentery, or peritoneal implants were also factors limiting resection.

The overall 5-year survival rate for patients with retroperitoneal sarcoma is 15% to 35%.^{24–26} This compares unfavorably with soft-tissue sarcoma of the extremity, which has a 5-year survival rate of 75% to 85%. Univariate analysis shows low-grade ($p < 0.001$), complete resection ($p < 0.001$), and age less than 53 years ($p < 0.05$) to be significant predictors of survival. Sex, size of primary, previous biopsy, histologic type, adjuvant therapy, and partial *versus* unresectable operation did not affect survival time.

Several staging systems have been proposed for soft-tissue sarcoma.²⁷ Each places appropriate emphasis on the grade of tumor. In this series patients with a high-grade sarcoma have a 25% 5-year survival rate compared to 65% for low-grade tumors. Similar results are reported in other series.^{19,24}

Complete resection of primary retroperitoneal sarcoma in this series led to an actuarial 5-year survival rate of 74%. Pooled data^{9,19–23,25} from 233 patients with completely resected primary soft tissue of the retroperitoneum shows ~50% 5-year survival. This is compared with 5-year survivals in this series after partial resection of 35% and unresectable disease of 15%. Other surgical series^{19–21} support the poor 5-year survival rate associated with partial resection (8% to 33%) and unresectable patients (3% to 10%).

All series of retroperitoneal sarcoma report high local recurrence rates ranging from 40% to 82%.^{19,21–24,28} With median time to recurrence of 15 months and 44 months for high- and low-grade tumors, a period of intense follow-up is defined. Patients are evaluated with physical examination every 2 to 3 months. Abdominal mass, pain, or other abdominal symptoms indicate the need for CT/MRI study. For the first 2 to 3 years, asymptomatic patients should have a CT or MRI scan at 6-month intervals to detect local recurrence. The recorded survival rates after complete resection of recurrent disease argue for surgical intervention at the time of diagnosis. Most of these patients were also symptomatic, affording an opportunity for palliation as well. The size of this series does not allow accurate assessment of the influence of lead time bias and its independent role in improved survival, or of whether in asymptomatic disease aggressive resection of CT identified disease necessarily improves survival.

With median follow-up of 31 months, 49% of patients in this series have experienced recurrence. Local recurrence is the predominant site of first recurrence (75%). These rates are compared to the reported 10% to 15% local recurrence rate associated with multimodality treatment of extremity soft-tissue sarcoma.^{28–31} There is potential survival benefit for improved local control of retroperitoneal sarcomas.³²

In the absence of distant metastases, patients with recurrent intra-abdominal disease are assessed for resectability and are surgically explored. Morbidity (24%) is comparable to operations for primary disease. A 6% operative mortality rate was observed, accounting for five of the six 30-day operative deaths in this series. Recurrent retroperitoneal sarcomas were resected completely in 44% of these operations. Grade, size, and histologic type do not predict resectability of recurrent disease and should not determine operability. Resection of adjacent organs should be anticipated. Median survival time after complete resection of recurrent disease is 48 months compared to 15 months for unresectable patients. Despite this, recurrent disease predicts further recurrences and ultimate death from disease. Fourteen to sixty-five (22%) patients who had operable recurrences are NED. The median survival from time of recurrence is 24 months.

High local recurrence rates for retroperitoneal sarcomas define a need for more effective local therapy. Experience with soft tissue sarcomas of the extremity argues for adjuvant radiotherapy for high-grade lesions.^{29,30} There is no prospective trial assessing efficacy of adjuvant radiation therapy for retroperitoneal sarcomas. Despite the use of 5400 rad postoperative adjuvant radiation therapy, the abdomen was the first site of recurrence in 69% of patients.²³ This is comparable to other surgery-only series.^{19–21} Major toxicity to retroperitoneal structures and severe radiation enteritis (15% to 22%) is reported.^{23,25}

TABLE 10. *Retroperitoneal Soft-tissue Sarcoma: Local Recurrence After Adjuvant Radiation Therapy*

Series	No. of Patients	Radiation Dose (rad)	% Local Recurrence
Cody ¹⁹ (MSKCC)	15	Unreported	66
Lindberg ³¹ (M. D. Anderson)	21	6000–7000	38
Glenn ²² (N.C.I.)	37	5400	30
Kinsella ²³ (N.C.I.)	35	2000 IORT + 3500 ERT or 5000–5500 ERT	51
Wist ²⁵ (Norway)	10	5000	50
Current series (MSKCC)	11	4500	45

Adjuvant radiation therapy was used in this series in 11 of 41 patients with completely resected primary disease. There has been no statistically significant overall or disease-free survival in the treatment group. These results are compared to other series reporting the use of adjuvant radiation therapy^{19,22,23,31,33} (Table 10). Timing of radiotherapy (pre- versus postoperative) and optimal dose have not been conclusively determined for retroperitoneal sarcomas.^{33,34}

Intraoperative radiation therapy (IORT) is feasible,^{35,36} although dose limitations are evident experimentally³⁷ and in clinical application.²³ A recent trial comparing IORT (2000 rad) and external radiation therapy (ERT) (3500 to 4000 rad) to ERT only (5000 to 5500 rad) showed no statistical difference in overall survival, disease-free survival, local control, or in-field control.²³ While the incidence of radiation enteritis was reduced, peripheral neuropathy was more frequent in the IORT group. The impracticality of the method of IORT makes this an unreasonable choice.

Adjunctive brachytherapy has been associated with a decrease in local recurrence after complete resection of high-grade extremity soft-tissue sarcoma.²⁹ Adjuvant brachytherapy was used in this series in four patients with retroperitoneal sarcoma with no unique toxicity. No improvement in survival or in local control could be ascertained from this limited experience. Large area of risk and proximity to major vascular structures may limit the application of adjuvant brachytherapy for retroperitoneal sarcoma. Other adjuvant modalities, including intraoperative photodynamic therapy³⁸ and hyperthermia,³⁹ have not yet been shown to be efficacious.

Radiation therapy for unresectable retroperitoneal sarcoma is associated with local progression of disease and death in all but the unusual case.^{25,33,40} It is reserved for selected palliative indications.

There is no evidence to support the use of adjuvant chemotherapy for retroperitoneal sarcoma.⁴¹ In one series a cohort of 37 patients with complete resection of high-grade retroperitoneal sarcoma received postoperative radiation therapy. Twenty-one of these patients were treated

with adjuvant chemotherapy (adriamycin, cytoxan, methotrexate) and 16 received no additional therapy.²² There was no improvement in disease-free survival or overall survival rate observed in the chemotherapy group. Major toxicity due to the chemotherapy was encountered in this protocol. Similar therapy did show improved survival time for extremity high-grade soft-tissue sarcoma.⁴² Other series have shown no improved survival with adjuvant chemotherapy for soft-tissue sarcoma.^{43,44} Neither series was large enough to comment on efficacy based on primary site. There was no apparent benefit accrued to 10 of 41 patients receiving adjuvant chemotherapy in this series. A phase I study evaluating toxicity of preoperative chemotherapy followed by resection of high-grade retroperitoneal sarcoma is now being investigated.

Adriamycin-based multidrug chemotherapy regimens are used in the treatment of unresectable or metastatic soft-tissue sarcoma. Considering all primary sites, complete response has been reported in 15% to 35% of patients.^{44–46} In this series, 29 patients received adriamycin-containing chemotherapy regimens and no complete responses were recorded.

In contrast to extremity soft-tissue sarcoma, sarcomas of the retroperitoneum are characterized by high local recurrence rates, more frequent hepatic metastases, and poor responsiveness to tolerable radiation doses and chemotherapy. The confines of the retroperitoneum limit the ability of the surgeon to perform a complete resection of the tumor without the frequent resection of adjacent organs or vascular structures. Both primary and recurrent soft-tissue sarcoma of the retroperitoneum can be completely resected in most patients, thus affording improved survival rates. The histologic grade of the tumor and the resectability are the significant predictors of outcome.

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Intra-abdominal Abscess After Blunt Abdominal Trauma

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The relationship between blunt abdominal trauma and intra-abdominal abscess (IAA) is discussed infrequently; therefore we conducted a retrospective review of 4050 multiple blunt trauma admissions from January 1986 to July 1988. Of 325 patients who had a laparotomy for blunt abdominal trauma, we identified 15 (4.6%) who had 40 IAAs. The most common intra-abdominal injuries involved the spleen and liver. Splenectomy increased the risk for IAA in contrast to splenic salvage. Blunt injuries to the kidney and pancreas, when occurring in multiple trauma patients, carried a significant risk of IAA. Associated multiple extra-abdominal injuries and high transfusion requirements increased the risk for IAA formation. Most of the IAAs were located in the upper quadrants. There was a 46% incidence of multiple IAA, which in turn had an 80% chance of recurrence after initial drainage. *Enterobacter* species played an important role in the formation of IAA in our trauma patients. Three patients (20%) died. Poor prognostic indicators included a high injury severity score, high transfusion requirements, the presence of pelvic fracture, positive blood cultures, multiple organisms per abscess, and multiple-organ system failure.

TRAUMA IS ONE of the leading causes of death in the United States today. In traumatized patients who survive longer than 3 days, infection becomes the primary cause of late death. Although intra-abdominal infection in our unit represents only 8% of all infections, it still carries a significant morbidity rate. Recent radiographic localization techniques have permitted the earlier diagnosis and treatment of patients with intra-abdominal abscesses (IAA), but mortality rates remain as high as 40%.¹ Intra-abdominal abscess after penetrating abdominal trauma has been well documented, with incidences ranging from 3.3% to 45%.²⁻⁴ However the relationship of blunt abdominal trauma and IAA has been seldom discussed; therefore we retrospectively reviewed our experience with IAA in patients who had sustained blunt abdominal trauma.

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Materials and Methods

Between January 1986 and July 1988, there were 4050 multiple blunt trauma admissions to our institution. The mechanisms of injury included motor vehicular accidents (MVA) (53%), falls (16%), motorcycle accidents (MCA) (9.3%), struck pedestrians (7%), and assaults (5.6%).

The trauma patients who are admitted to our unit undergo initial evaluation and spine immobilization, and aggressive fluid resuscitation is started when indicated. Type O unmatched blood is given to those patients who remain hypotensive (blood pressure [BP] less than 90) despite administration of 2 L of crystalloid infusion. All patients undergo radiographic evaluation of the cervical spine, chest, and pelvis. An abdominal examination follows; if evidence of peritonitis is present, these patients are explored. Patients with equivocal findings are further investigated by diagnostic peritoneal lavage (DPL) or computed tomography (CT) scan. A positive DPL is defined by the aspiration of 20 mL of gross blood from the peritoneal cavity or more than 100,000 red blood cells/cm³ in the lavage effluent.

Once the decision is made to proceed with exploratory celiotomy, either cefazolin or cefoxitin is given prophylactically and continued for three doses after operation. If the bowel wall is noted to be injured, cefoxitin is given during operation as the preferred antimicrobial agent. The abdomen is explored in the usual manner through a midline incision, with four-quadrant packing, evisceration, and aspiration of intraperitoneal blood. Control of active hemorrhage is the first priority, followed by control of bowel contents. Standard techniques for hemostasis and organ repair are then applied. Closed suction drainage systems are used when indicated and are removed when

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the volume of the drainage has decreased, except when placed for pancreatic injuries—in this case, the drainage system remains in place for at least 1 week. A modified trauma score (TS) and injury severity score (ISS) are calculated.^{5,6}

During the next few days, these patients are followed closely by the surgical and infectious disease staff. An infectious disease team follows all critical care patients at our center daily, closely monitoring temperature, white blood cell (WBC) counts, renal function, hepatic function, and the clinical status of the patient. Detailed microbiologic surveillance data are obtained and reviewed. If various parameters make us suspicious of an infectious process, then diagnostic studies are begun. To diagnose IAA we depend on physical examination, ultrasound examination, CT scan, and, rarely, paracentesis. Using these methods we identified 15 patients who developed IAA during the study period. A diagnosis of IAA was made when organisms were isolated from intra-abdominal collections gathered at surgery or by needle aspiration. We also included patients with organisms isolated from free peritoneal fluid. Three cases of acute cholecystitis were not included in this review. The criteria for organ failure as described by Fry⁷ were applied.

Results

Of 4050 patients admitted to our center with blunt trauma, 325 (8%) underwent exploratory celiotomy. The mean TS and ISS for that subgroup were 14 ± 2 and 34.5 ± 15 , respectively. Among the 325 patients with blunt abdominal trauma, 129 splenic injuries were detected, 83 of which required splenectomy. Other abdominal injuries are listed in Table 1.

Twenty-three IAA developed in 15 (4.6%) of the 325 patients who underwent celiotomy. This procedure was performed in 14 of them within 24 hours of admission. The mechanism of injury in this group was MVA in 12, struck pedestrian in 2, and MCA in 1. Ten patients were men and 5 were women. The ages ranged from 18 to 68 years (mean, 33 years). Five patients presented with a systolic BP ≤ 90 mmHg. The TS was available in 11 patients, and the average score was 11.8. The mean ISS of this group was 45.6. Thirteen patients had two or more intra-abdominal injuries (Table 1). Eight patients underwent splenectomy, including one done on hospital day 2 and another on hospital day 48 for a delayed rupture. Angiographic embolization was done for a renal artery injury and for a lacerated pelvic artery to control hemorrhage. All patients had at least one major extra-abdominal injury. These included injuries of the chest (10), pelvic ring (8), long bones (6), brain (8), and cervical spinal cord (1). The amount of blood transfused within the first 24 hours ranged from 3 to 77 units in 12 patients, with a mean of 22 units per patient.

TABLE 1. Injuries

	All Laparotomies for Blunt Abdominal Trauma (n = 325)	Patients with IAA (% of injuries) (n = 15)
Mean TS	14 ± 2	11.8 (11 patients)
Mean ISS	34.5 ± 15	45.6
Intra-abdominal injuries		
Spleen*	129	9 (6.9)
Liver	112	9 (8)
Pancreas	22	3 (13.6)
Renal	22	3 (13.6)
Small bowel	45	2 (4)
Urinary bladder	24	2 (8)
Colon	43	1 (2)
Biliary tract	Not available	1
Stomach	Not available	1

* The spleen was salvaged in 46 of 325 patients; 1 (2%) developed IAA. Splenectomy was necessary in 83 of 325 patients; 8 (9.6%) developed IAA.

The clinical signs of sepsis were present as early as the second postoperative day and as late as day 16 (mean, 7.8 days). The WBC count ranged from 12,300 to 40,000, with a mean of 22,600. The average temperature was 102.6 F when sepsis was first suspected. Only one patient had a tender abdomen at examination. Four patients presented with wound infections or dehiscence. One patient had frank pus coming from a drain site. All patients had abnormal chest radiographs. Unilateral pleural effusions or basilar atelectasis, which later coincided with subphrenic abscesses, were seen in five instances. Three patients had positive blood cultures for enteric organisms (Group D enterococci, *Escherichia coli*, *Pseudomonas* species, *Bacteroides* species).

Computed tomographic scan abnormalities consistent with abscess were found in 11 of the 12 patients in whom this procedure was performed in the initial evaluation. The patient with a false-negative scan had a right subhepatic abscess seen on sonography. Ultrasound examination was used for diagnosis in one patient. Another underwent nondirected exploratory laparotomy after blood cultures grew *Bacteroides fragilis*. The 15th patient had needle aspiration of infected ascitic fluid and was treated with antibiotics only, not with drainage.

In three patients radiographic-guided percutaneous aspiration of suspicious collections helped make the diagnosis. Percutaneous catheter drainage (PD) of IAA was successful as the initial treatment in 2 of 3 patients, and surgical drainage was successful in 7 of 11.

The majority (82%) of IAAs were intraperitoneal, with most of them located in the upper quadrants (Table 2). Five patients had single organisms isolated from the IAA (*Enterobacter*, 2; *E. coli*, 1; *Serratia*, 1; and *Candida* species, 1). The other patients (10) had multiple organisms, with an average of 2.9 organisms per patient (Table 3).

TABLE 2. Location of IAA (40) Secondary to Blunt Trauma*

	Initial (%)	Recurrent (%)
Intraperitoneal		
Right upper quadrant	7 (30)	5 (29.4)
Left upper quadrant	5 (21.7)	5 (29.4)
Left paracolic	2 (8.6)	2 (11.7)
Interloop	2 (8.6)	
Lesser sac	1 (4.3)	1 (5.8)
Right paracolic	1 (4.3)	1 (5.8)
General peritonitis	1 (4.3)	
Subtotal	19 (82.6)	14 (82)
Retroperitoneal		
Pelvic	1 (4.3)	
Visceral		
Renal	1 (4.3)	
Hepatic	1 (4.3)	2 (11.7)
Pancreas	1 (4.3)	1 (5.8)
Subtotal	3 (13)	3 (17)
Total	23 (100)	17 (100)

* Table format adapted from Altemeier WA, et al. Intra-abdominal abscesses. Am J Surg 1973, 125:70-79.

Bacteroides species were seen in three patients. Five patients developed a total of 17 recurrent IAA. Successful drainage of recurrent IAA required a total of 14 procedures (PD in seven instances and surgical drainage in seven instances).

Twelve patients survived. Their length of stay (LOS) ranged from 39 to 152 days (mean, 82 days). Complications in these patients included adult respiratory distress syndrome (ARDS) (5), urinary tract infection (5), pneumonia (4), enterocutaneous fistulae (2), pancreatic fistula (1), and intravascular catheter-related sepsis (2). Their average ISS was 42.8, and the mean first 24-hour transfusion requirement was 18.6 units.

Three patients died. Their LOS ranged from 13 to 20 days (mean, 16 days). They all developed multiple-organ systems failure (MOSF). All had ARDS, liver failure, and renal failure. Two patients had disseminated intravascular coagulation (DIC) and one had cerebral infarction, which progressed to brain death. The average ISS for this group was 57 and the mean first 24-hour transfusion requirement was 33 units. Two of these three patients had positive blood cultures (*Enterobacter* species, *Bacteroides fragilis*, *Pseudomonas* species, and *E. coli*). One developed IAA associated with a leaking small bowel anastomosis. Another patient had an avulsed gallbladder at the initial operation, which may have been colonized. The third patient developed early MOSF with DIC, causing thrombosis of her brachial artery, which required an amputation. Her ascitic fluid was apparently hematogenously infected with *Enterobacter*, *Klebsiella*, and *Serratia*.

Discussion

Sepsis continues to be a primary cause of late death in the multiply injured patient. Although the risk of IAA

after penetrating abdominal trauma has been described in several series, the risk of IAA after blunt abdominal trauma is not well documented. The incidence of IAA after penetrating abdominal trauma ranges from 3.3% to 45%.²⁻⁴ Ivatory² reported an incidence of 3.3% in 872 patients who had sustained penetrating abdominal trauma. This rate increased to 6% when he considered only gunshot wounds. Our incidence of 4.6% is comparable, although only 25.2% of our patients had injury to the gastrointestinal tract. The incidence of IAA in those patients who have sustained penetrating abdominal trauma without bowel injury is negligible.⁸

The mean TS and ISS for patients undergoing celiotomy were 14 ± 2 and 34.5 ± 15 , respectively, compared with 11.8 and 45.6 in the 15 patients who developed IAA. A TS less than 11 and an ISS greater than 40 are associated with mortality rates of at least 22.8% and 34.5% at our institution.^{5,6} All of our patients had at least one serious extra-abdominal injury. Chest injuries predominated and included such injuries as multiple rib fractures, pulmonary contusion, ruptured thoracic aorta, and ruptured diaphragm. There were eight pelvic ring disruptions, which implies a significant impact of blunt force.

The mean transfusion requirement for the first 24 hours for our group of patients with IAA was 22 units (12 patients). Nichols⁸ showed that the odds of a postoperative infection increased with each 10 units of blood. Infected patients in Dellinger's series had received 10.8 ± 12 units of blood for resuscitation after abdominal trauma.³ Scott's study⁹ demonstrated that the risk of developing an intra-abdominal septic focus exceeded 50% when transfusion requirements were 23 units or more. All these studies conclude that a prime determinant of abscess formation was the increased blood transfusion requirement and that blunt trauma increases the risk of abscess formation compared to penetrating injury because of greater blood losses.

Most of our patients sustained injuries to the spleen and liver (9 patients each), as would be expected in blunt

TABLE 3. Bacteriology

Organism	Number of Isolates (% of total)
Aerobic	
<i>Enterobacter</i>	10 (28.5)
<i>Escherichia coli</i>	5 (14.2)
Other gram-negative rods*	9 (25.7)
Streptococci†	5 (14.2)
<i>Staphylococcus epidermidis</i>	2 (5.7)
Subtotal	31
Anaerobic	
<i>Bacteroides fragilis</i>	3 (8.8)
<i>Candida</i> species	1 (2.8)

* Includes *Pseudomonas* (3), *Acinetobacter* (2), *Citrobacter* (1), *Klebsiella* (1), *Proteus* (1), and *Serratia* (1).

† Includes *Streptococcus pyogenes* (2) and group D enterococci (3).

trauma. Eighty-three patients underwent splenectomy, eight (9.6%) of whom developed IAA. Only one (2%) patient who had a splenic salvage procedure developed an IAA. Ellison's review¹⁰ showed that splenectomy posed a risk for a subphrenic abscess in 3.4% to 10% of cases and that risk increased if there was an associated bowel injury or if drains were used.

In liver trauma, intra-abdominal sepsis is second to exsanguination as the leading cause of death and it is a primary cause of late death. Intra-abdominal abscess occurred in 17% of Scott's series⁹ of patients who had sustained hepatic trauma. The need for hepatic resection, perihepatic packing, the presence of associated gastrointestinal tract injury, and the use of open drainage systems have all been implicated in the formation of IAA. In reviewing 770 patients from several major trauma centers, who had sustained liver trauma with blunt trauma, comprising 32% of cases, Moore¹¹ found a perihepatic abscess rate of only 4%. Feliciano¹² reported a 10.2% incidence of perihepatic abscess formation after perihepatic packing for hemorrhage in 58 patients. Nine (8%) patients with a total of 112 liver injuries developed IAA in our series; two of them required perihepatic packing to control hemorrhage.

Three (13%) patients with pancreatic injuries developed pancreatic abscesses. Pancreatic fistulae and/or abscesses developed in 29.3% and 7% of patients with pancreatic trauma in Sims'¹³ and Stone's¹⁴ series, respectively.

The three (13%) patients with renal injuries developed perirenal abscesses that were all associated with hematomas. One of these patients underwent renal artery embolization to control bleeding. The second patient developed an infected pelvic hematoma after a urinary bladder rupture and the third had a pelvic fracture that needed transcatheter embolization of pelvic vessels to control hemorrhage.

Hematoma and its hemoglobin content have been implicated in the development of intra-abdominal sepsis. Not only does the plasma provide a medium for bacterial growth but also the hemoglobin inhibits bacterial absorption from the peritoneal cavity, polymorphonuclear leukocyte chemotaxis, and intracellular killing.¹⁵ The use of transcatheter gelfoam embolization for retroperitoneal or pelvic hemorrhage and its potential for ischemia have been documented.¹⁶ The presence of ischemia, hematoma, and tissue injury secondary to trauma could increase the risk of secondary infection.

The elevated temperature and WBC count seen in our patients are consistent with other series of IAA.¹⁷ One (6%) patient had a tender abdomen on examination and 4 (26.6%) patients presented with wound infections and/or dehiscence. Others have reported that physical examination may aid in the diagnosis of IAA in as many as 25% to 60% of patients.¹⁸⁻²¹ Ipsilateral pleural effusion or

basilar atelectasis is a nonspecific sign of intra-abdominal pathology and was present in 5 of 13 (38%) patients who had upper quadrant collections. Some report that plain radiographs may be helpful in at least 50% to 75% cases of IAA.^{4,21,22}

More than one half (62.5%) of all IAAs were located in the upper quadrants. This could be related to the larger number of liver and splenic injuries and the cephalad flow of peritoneal fluid. Seventy-five per cent of Ivatory's patients had IAA in the upper quadrants after penetrating abdominal trauma.² Multiple intra-abdominal abscesses were discovered on initial laparotomy in 7 (46.6%) patients, with an average of two abscesses per patient. The reported incidence of multiple abscesses ranges from 8% to 31%.¹⁹⁻²¹

We relied on CT examination to aid in the diagnosis of IAA and it was positive in 11 of 12 attempts (91%), which is consistent with other series.^{18,20} Ultrasound examination was helpful in three patients and identified a subhepatic collection not seen on CT scan; two of these patients had collections in the right upper quadrant and one had a collection in the left upper quadrant. Computed tomography and ultrasound-guided needle aspiration were accomplished in two patients each. One patient had a peritoneal tap at the bedside to diagnose infected ascitic fluid, and the remaining patient who developed MOSF underwent exploratory laparotomy after positive blood cultures were obtained.

Percutaneous catheter drainage was attempted in only three patients, using sonography once and CT guidance twice, and was initially successful in two patients who had single subphrenic abscesses. Deveney²⁰ concluded that PD may be superior to surgical drainage for subphrenic abscesses. Although it has been reported that 50% of patients with IAA are candidates for PD, our rate of use was only 37.5% (three of eight patients) if we include only those patients with single abscesses.²³ This may be due to the high incidence of associated infected hematoma in our patients. Initial surgical drainage was successful in 7 of 11 (63%) patients. Our overall initial success rate in the treatment of IAA is somewhat lower (60%) than other series, which report success rates close to 80%.^{18,20,23-25} This could be related to the high incidence of multiple injuries and multiple abscesses in our study group.

Seventy per cent of the organisms isolated from IAA were aerobic gram-negative rods, with *Enterobacter* species comprising more than 29% of all strains. This is in contrast to the predominance of *E. coli* seen in IAA secondary to all causes.¹⁷ The predominance of *Enterobacter* species in our series may be related to prophylactic use of cefazolin and cefoxitin, which may select out this organism, as reported in other series.^{2,8} This organism is also the predominant gram-negative pathogen in catheter-related sepsis and other infections at our institution. *En-*

terobacter made up 32% of the organisms isolated in Ivatory's series. *Enterococcus* species were seen in three patients who also had other organisms isolated (mean of four organisms per patient). *Staphylococcus epidermidis* and non-group D streptococci comprised 11% of strains isolated. The etiology of these as intra-abdominal pathogens may be related to poor skin preparation during the initial laparotomy. Three (20%) patients had enteric organisms isolated from blood cultures. Butler¹⁹ obtained positive blood cultures in 31% of his patients with IAA. The presence of multiple enteric organisms cultured from the blood was associated with an intra-abdominal source of sepsis in 78% of patients in Ing's series.²⁶

Recurrent abscesses occurred in 5 (41.6%) of the 12 patients who survived, requiring 14 more drainage procedures before resolution. Four (80%) of these patients had multiple IAAs at relaparotomy. There was only one (14%) recurrence in the remaining seven patients who had a single abscess. This is consistent with Aeder's²⁵ recurrent abscess rate of 10% in patients with single abscesses. Deveney²⁰ had a 50% to 60% initial drainage success rate for his 12 patients with multiple IAAs treated surgically. Those patients with single abscesses had an average of 1.6 organisms isolated and an average length of stay of 60 days, whereas those with multiple abscesses averaged 2.1 organisms and 111 days in the hospital.

There were three deaths (20% mortality rate) in this series, which is consistent with other series in which mortality rates range from 17% to 30%.^{2,18-21} In his series of 143 abscesses (40% of which were due to trauma), Fry²¹ concluded that organ failure, lesser sac abscess, positive blood cultures, recurrent or persistent abscess, multiple abscesses, age more than 50 years, and subhepatic abscesses increased the risk of death. Butler¹⁹ added the need for nondirected exploration as a risk for death. Ivatory² reported a 50% mortality rate in his patients who had MOSF. These patients had a higher abdominal trauma index score, a greater transfusion requirement, and a greater number of organs injured than did the non-MOSF group. Our data, summarized in Table 4, are consistent with those of others. The patients in the nonsurvivor group were older (40 versus 30 years) and had higher ISS (57 versus 42), with more intra-abdominal injuries (3 versus 2.3) and more extra-abdominal injuries (3.3 versus 2.3), along with a greater first 24-hour blood transfusion requirement (33 versus 18.6 units). Five of the survivors (42%) and all of the nonsurvivors suffered pelvic ring disruption. Multiple-organ system failure was the mode of sepsis presentation for all the nonsurvivors. A different modality was used to diagnose IAA in each of the nonsurvivors: CT scan, ascitic fluid aspiration, and nondirected laparotomy. The time of onset of sepsis was less in the nonsurvivor group (6 versus 8.3 days); multiple abscesses were present in the nonsurvivor group (66.6%)

TABLE 4. Comparison of Survivors and Nonsurvivors

	Survivors	Nonsurvivors
No. of patients	12	3
Age (mean)	30.4	40.6
TS (mean)	12.4 (8 patients)	10.3
ISS (mean)	42.8	57
No. of intra-abdominal injuries (mean)	2.3	3
No. of extra-abdominal injuries (mean)	2.3	3.3
No. with associated pelvic fractures	5 (41%)	3 (100%)
First 24-hour transfusion requirement (mean)	18.6 units (9 patients)	33 units
Initial presentation (days)	8.3	6
Positive blood cultures (%)	1 (8.3%)	2 (66.6%)*
No. of organisms isolated (mean) per patient	1.75	4
No. of patients with multiple abscesses	5 (42%)	2 (66.6%)
Organ failure		
ARDS	5 (42%)	3 (100%)
Hepatic	0	3 (100%)
Renal	0	3 (100%)
DIC	0	2 (66.6%)
Cerebral infarction	0	1 (33.3%)
Length of hospitalization	82 days	16 days

TS, Trauma Score; ISS, Injury Severity Score; ARDS, adult respiratory distress syndrome; DIC, disseminated intravascular coagulation.

* $\chi^2 = 4.8$; $p < 0.05$.

and the survivor group (42%); blood cultures were more often positive ($p < 0.05$) in the nonsurvivor group (2 patients) versus the survivor group (1 patient); and a mean of four organisms per abscess was isolated in the nonsurvivor group versus 1.75 organisms in the survivor group.

In the survivor group, five patients developed single organ failure, all manifested by ARDS, and all survived despite a reported mortality rate of ARDS as high as 67%.^{7,21,27} All three patients who developed MOSF died (all had ARDS, hepatic failure, and renal failure). The reported mortality rate among patients with three-organ failure surpasses 75%.^{7,27}

Several series report the incidence of MOSF after IAA. Forty-four per cent of Fry's²⁷ 38 patients had MOSF; Ferraris²⁸ found that 80% of his 29 postoperative patients with either MOSF or single-organ failure had IAA; and Polk²⁹ explored 11 patients for MOSF and drainable collections of pus were found in 6 (55%). These studies conclude that, in patients with MOSF, a high index of suspicion for an intra-abdominal source of sepsis is warranted. The survival rate for those without and with drainable sources of infection was 18% and 33%, respectively.¹ Bunt³⁰ believed that the yield was low for nondirected laparotomies in critically ill patients with MOSF; it was well tolerated by the young trauma patient and probably should be avoided in the elderly. He reported

an overall positive laparotomy rate of 63% in patients with MOSF. Those patients undergoing directed laparotomies had a 94% positive laparotomy rate, whereas only 13% of those with nondirected laparotomies had positive findings. Norton³¹ concluded that MOSF secondary to IAA carried a high mortality rate (76%) and that surgical drainage will not reverse organ failure in most patients. Autopsy of the 16 patients who died demonstrated a persistent septic focus in only 3 (19%). Perioperative mortality rates in septic patients with MOSF undergoing relaparotomy ranges from 70% to 90%, regardless of whether a septic focus is found.^{1,2,19,30}

Intra-abdominal abscess developed in 4.6% of our patients undergoing emergency laparotomy for blunt abdominal trauma. Most IAAs due to blunt abdominal trauma are located in the upper quadrants. Associated multiple extra-abdominal injuries and high transfusion requirements increase the risk of IAA formation.

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Preoperative Characteristics Predicting Intraoperative Hypotension and Hypertension Among Hypertensives and Diabetics Undergoing Noncardiac Surgery

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We prospectively studied patients with hypertension and diabetes undergoing elective noncardiac surgery with general anesthesia to test the hypothesis that patients at high risk for prognostically significant intraoperative hemodynamic instability could be identified by their preoperative characteristics. Specifically we hypothesized that patients with a low functional capacity, decreased plasma volume, or significant cardiac comorbidity would be at high risk for intraoperative hypotension and those with a history of severe hypertension would be at risk for intraoperative hypertension. Patients who had a preoperative mean arterial pressure (MAP) ≥ 110 , a walking distance of less than 400 m, or a plasma volume less than 3000 cc were at increased risk of intraoperative hypotension (*i.e.*, more than 1 hour of ≥ 20 mmHg decreases in the MAP). Hypotension was also more common among patients having intra-abdominal or vascular surgery, and among those who had operations longer than 2 hours. Patients older than 70 years or with a decreased plasma volume were at increased risk of having more than 15 minutes of intraoperative elevations of ≥ 20 mmHg over the preoperative MAP in combination with intraoperative hypotension; this was also more common when surgery lasted more than 2 hours. Patients who had intraoperative hypotension tended to have an immediate decrease in MAP at the onset of anesthesia and were often purposefully maintained at MAPs less than their usual level during surgery with fentanyl and neuromuscular blocking agents. Patients who had intraoperative hyper/hypotension tended to have repeated elevations in MAP above their preoperative levels during the course of surgery, and such elevations precipitated interventions with neuromuscular blocking agents and/or fentanyl. Neither pattern was more common among patients who developed net intraoperative negative fluid balances. Both hypotension and hyper/hypotension were associated with increased renal and

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cardiac complications after operation. Patients with cardiac disease, especially diabetics, and those with negative fluid balances also had increased complications. Preoperative characteristics influence the susceptibility to intraoperative hypotension and hypertension, which are related to postoperative complications.

WHILE MOST STUDIES have demonstrated that intraoperative hypotension increases the risk of postoperative cardiac¹⁻⁵ and renal^{6,7} complications, there is less agreement about the impact of other intraoperative hemodynamic patterns (*e.g.*, hypertension alone or hypertension and hypotension).⁸⁻¹⁰ We have shown that patients with hypertension or diabetes whose intraoperative mean arterial pressure (MAP) decreased ≥ 20 mmHg below their preoperative MAP for more than 1 hour had increased cardiac and renal complications.¹¹⁻¹³ In addition patients who experienced both 15 minutes or more of elevated MAP (≥ 20 mm above their usual MAP) and less than 1 hour of ≥ 20 mmHg decreases in their MAP hour had increased complications.¹¹⁻¹⁴ Together these two patterns, which will be called intraoperative hypotension and intraoperative hyper/hypotension, respectively, had a 46% sensitivity rate and a 70% specificity rate as predictors of postoperative complications.

There has been no reliable method of identifying patients at risk for intraoperative hypotension, hypertension, or both. Furthermore it has not been possible to distinguish patients specifically at risk for intraoperative hypotension as opposed to hypertension, which clearly would have importance for patient management, because strategies to prevent intraoperative hypotension may differ substantially from those designed to prevent hypertension.

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The explicit prior hypothesis of this study was that patients at high risk for significant episodes of intraoperative hypotension or hypertension could be identified by their preoperative characteristics. Specifically patients with a low functional capacity, decreased plasma volume, or significant cardiac comorbidity were hypothesized to be at high risk for intraoperative hypotension and those with a history of severe hypertension were hypothesized to be at risk for intraoperative hypertension. The purpose of this analysis was to test this hypothesis. The intraoperative management of patients with hypotension, hypertension/hypotension, or those without either of these high-risk patterns was also examined to develop a qualitative context for the evaluation of these intraoperative hemodynamic patterns.

Methods

Assembly of Population

All patients who had essential hypertension or diabetes who were undergoing elective general surgery were eligible for enrollment. The criteria for hypertension were (1) for patients younger than 30 years, systolic ≥ 150 mmHg or diastolic ≥ 90 mmHg; (2) for patients 30 years or older, systolic ≥ 160 mmHg or diastolic ≥ 95 mmHg; or (3) treatment with any medication explicitly used to reduce blood pressure (*i.e.*, patients treated with diuretics for congestive heart failure alone were not considered hypertensive). The criteria for diabetes were (1) treatment with insulin or oral hypoglycemic agents, including treatment started during hospitalization, and (2) elevated fasting glucose on more than one occasion (plasma ≥ 140 mg/dL; whole blood ≥ 120 mg/dL).

Between July 1982 and September 1985, 278 patients were enrolled in our study. To document the proportion of eligible patients who were entered into the study, the charts of all 1398 patients undergoing several types of operation (vascular surgery or cholecystectomy) during the same secular interval were reviewed; these operations accounted for 40% of the surgery performed in the prospective study. In these groups 26% of eligible hypertensives and 34% of eligible diabetics had been entered into the prospective study.¹³

Preoperative Evaluation

The protocol was reviewed and approved by the Institutional Human Rights Committee. Informed consent was obtained on all patients. Before operation basic demographic and clinical data were recorded and a physical examination focused on abnormalities in the pulmonary, cardiac, neurologic, and vascular systems. The history of comorbid conditions was obtained using standardized questions and criteria.

Angina was defined as definite or probable according

to the Rose criteria.¹⁵ Patients with nocturnal or rest angina, or with a crescendo pattern, were designated as having unstable angina.¹⁵ Myocardial infarction included patients who had been hospitalized for chest pain and developed either new Q waves in at least two leads that were 0.04 seconds in duration and 1 mm in depth, new ST segment depression of 1 mm or more, or new T wave inversion that persisted for 7 days, with elevation of creatine kinase (CK) or CK-MB isoenzyme. Congestive heart failure included patients with a definite history of pulmonary edema, paroxysmal nocturnal dyspnea, or dyspnea on exertion,¹⁵ not in the setting of an acute myocardial infarction, arrhythmia, sepsis, and so on who responded to treatment and who required continued pharmacologic therapy. Patients with documented valvular disease of any type (aortic, mitral, prosthetic valve, and so on), except mitral valve prolapse, were defined as having valvular heart disease. Aortic valvular disease included two patients with previously documented hemodynamically insignificant aortic stenosis, 14 patients with grade ii/vi or louder systolic ejection murmur radiating to the carotids, and two patients with aortic insufficiency. Mitral valvular disease included two patients with previously documented mitral regurgitation and seven patients with grade ii/vi or louder holosystolic murmur radiating to the axilla. Patients were also classified according to Goldman's cardiac risk classification.¹⁶ Patients were classified as having severe hypertension if they had a history of diastolic blood pressure more than 120 mmHg or had been hospitalized for control of blood pressure. Chronic pulmonary disease included patients with chronic bronchitis¹⁵ and patients with a definite history of asthma that occurred without upper respiratory tract infections and that required pharmacologic treatment.

The patient's right and left arm sitting blood pressure and pulse, as well as the recumbent and standing pulse and blood pressure, were obtained. Blood pressure was recorded using a standard mercury manometer¹⁷ and Korotkoff phase V was recorded as the diastolic pressure. Blood pressures were obtained every 4 hours before surgery by the nursing staff. These systolic and diastolic blood pressures were recorded to delineate the patient's usual preoperative MAP. A 12-minute walking distance test was performed with encouragement whenever possible before operation.¹⁸⁻²⁰ Basic preoperative laboratory values were recorded, including hemoglobin, electrolytes, urinalysis, creatinine, creatine kinase, electrocardiogram, and chest x-ray. Cardiomegaly was present when the heart was labeled by the radiologist as definitely enlarged. An abnormal electrocardiogram included bundle branch block, definite or probable evidence of an old infarction, or definite left ventricular hypertrophy. Plasma volume was determined whenever possible using Evans blue²¹ 12 hours before operation; results were available for 50 patients.

Intraoperative Monitoring

On the day of surgery, a research assistant, blinded to the specific hypotheses of the study, recorded pulse and blood pressure during induction and intubation and every 5 minutes thereafter, using either an intra-arterial catheter (at the discretion of the anesthesiologist), a mercury manometer, or an indirect automatic device. In 52 patients intra-arterial measurements were made using a 20-gauge teflon catheter in the radial artery and connected to a Marquette 7000 dual pressure monitor (Marquette Electronics, Milwaukee, WI) calibrated before each use (accuracy of ± 1 mmHg). In 76 patients the Omega 1000 (Vivo Research Labs, Tulsa, OK), an indirect oscillometric blood pressure recorder was used (accuracy of ± 2 mmHg); the large adult cuff (15×33 cm) was used if the arm circumference was 30 cm or larger. The oscillometric device has been shown to produce reproducible and valid measurements of blood pressure while used in the operating room.²² In 150 patients the anesthesiologist used a standard mercury manometer instead of the Omega 1000. In these cases the research assistant obtained and recorded the blood pressures according to the procedures described previously. To standardize the definition of the MAP with the different techniques, MAPs were calculated as the diastolic pressure + $1/3$ (systolic - diastolic.) The primary analysis of intraoperative blood pressures was based on the differences between the intraoperative MAPs and the preoperative MAPs, after adjusting for differences between arms.

The research assistant recorded all pharmacologic agents used during each 5-minute interval of the operation. The use of anesthetic agents and adjuvants was recorded. Major intraoperative events, such as skin incision, reversal of anesthesia, aortic cross-clamping, drainage of ascites, and changes in position, were also recorded.

In 24 (8.6%) of the patients, the research assistant was not present in the operating room to record events and blood pressures. Because the purpose of this analysis is to assess preoperative predictors of high-risk intraoperative hemodynamic patterns, we have omitted these 24 patients (seven of whom had complications) because the intraoperative data was not recorded by an independent observer. Of these 254 patients, 47 patients had either local/regional or spinal/epidural anesthesia; 11 of these patients had complications. The rest of the paper will focus on the 207 patients who had general anesthesia.

Postoperative Follow-up

All patients were followed daily for 7 days after operation or until death, discharge, or reoperation with clinical examinations, serum creatinine tests, electrocardiograms, and creatine kinase isoenzyme tests. Patients who underwent reoperation were considered censored in terms of follow-up at the time of reoperation. The postoperative

course of any patient who developed dyspnea, palpitations, chest pain, signs of congestive failure, electrocardiographic changes, or increased serum creatinine level was reviewed by two physicians who were blinded to the patient's preoperative status and intraoperative course. These physicians determined whether the patients who were suspected of having myocardial ischemia, congestive heart failure, or postoperative renal impairment met the diagnostic criteria.²³

Definition of Outcomes

Life-threatening events. A total of eight patients had cardiac death, acute pulmonary edema, cardiac arrest, or myocardial infarction. There were two cardiac deaths, of which one occurred after intraoperative ventricular tachycardia, and one after an anginal episode. One cardiac arrest that did not lead to cardiac death occurred in the setting of pulmonary edema (pulmonary capillary wedge pressure more than 20 cm and a typical roentgenologic picture) and symptomatic myocardial ischemia. Two arrests occurred in the setting of a myocardial infarction: one with ST-T depression ≥ 48 hours with 12% MB (definite) and the other with ST elevation less than 48 hours with 6% MB (possible). In addition there was one definite myocardial infarction without an arrest or death and two patients with probable myocardial infarction: one patient had new T inversion of more than 48 hours with 25% MB and another had new T inversions of more than 48 hours with 8% MB.

Other cardiac complications. There was one patient with a possible myocardial infarction and 18 patients with definite ischemia with ECG changes. Twelve of these patients had elevated CK-MB, and the seven patients without elevated CK-MB had ST-T changes that persisted for more than 48 hours. In addition one patient had unstable angina without ECG changes and two patients had definite angina by the Rose criteria. Seven patients had postoperative congestive heart failure with at least two of the following: S3 gallop, typical roentgenologic picture, bibasilar rales involving more than one third of the lung fields, or an elevated central venous pressure (more than 18 cm of water).

Renal complications. Fourteen patients had postoperative renal dysfunction, *e.g.*, an increase in the serum creatinine of $\geq 20\%$ that persisted for 48 hours or more and that began in the first 3 days after surgery. In identifying patients whose serum creatinines remained persistently elevated at discharge from the hospital, an increase in the serum creatinine of $\geq 20\%$ persisting for more than 48 hours had a true-positive rate of 93%.²⁴

There were 48 complications in 44 patients; 4 patients had both postoperative renal dysfunction and congestive failure, and 4 had myocardial ischemia and congestive failure.

Data Analysis

Logistic regression was performed with the PROC LOGIST program in SAS²⁵ to determine differences between those patients with and without a given high-risk pattern according to the preoperative characteristics. An effort was made to constrain the number of variables entered into the model so that one covariate was entered for each 5 to 10 outcome events.²⁶ In the analysis of walking distance, patients who were unable to complete the test were combined with those who were able to walk more than 640 m because there were no significant differences between the groups. The logistic regression results, while reported in different sections of the paper, were obtained from a single equation, with six variables entered for hypotension, and five for hyper/hypotension. Because plasma volume was assessed in only 50 of the 207 patients, the logistic regression was performed using only those covariates that were significant predictors of hypotension or hyper/hypotension in the 207 patients as a whole.

Results

Of the total 207 patients, 41 (20%) had intraoperative hypotension: a ≥ 20 mmHg decrease from their usual preoperative MAP that lasted for 1 hour or more. An additional 39 (18%) patients had intraoperative hyper/hypotension: ≥ 15 minutes of hypertension with a ≥ 20 mmHg increase above their usual MAP in combination with a ≥ 20 mmHg decrease in their MAP lasting less than 1 hour. The remaining 127 (62%) patients had neither high-risk pattern.

As mentioned previously, intraoperative hypotension and hyper/hypotension had been identified as predictors of specific postoperative complications: renal dysfunction, myocardial ischemia, or infarction and congestive failure. Of the 207 patients, 44 had complications: 8 life-threat-

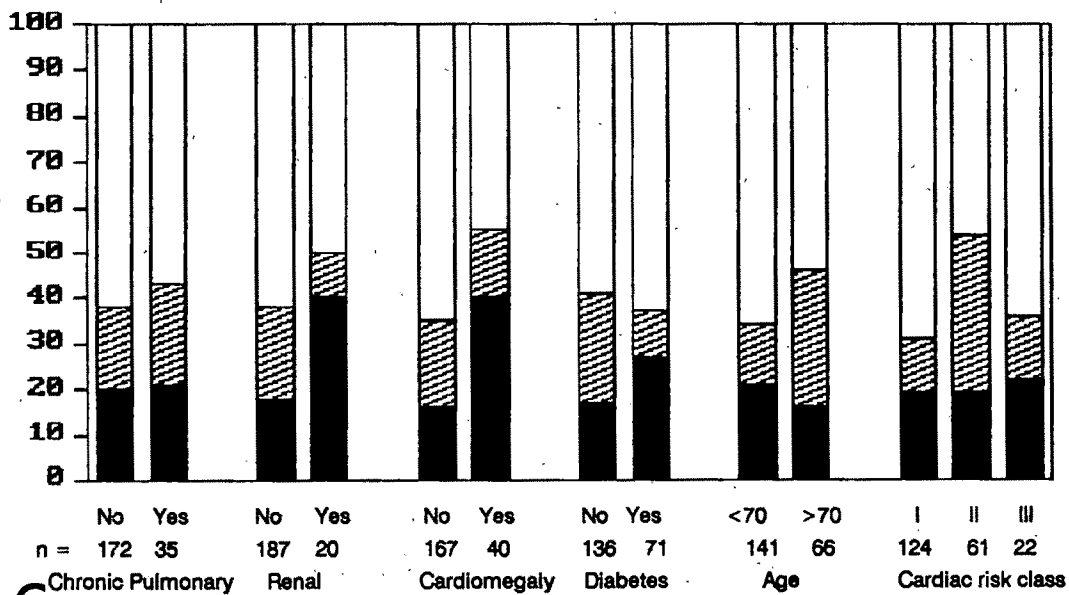
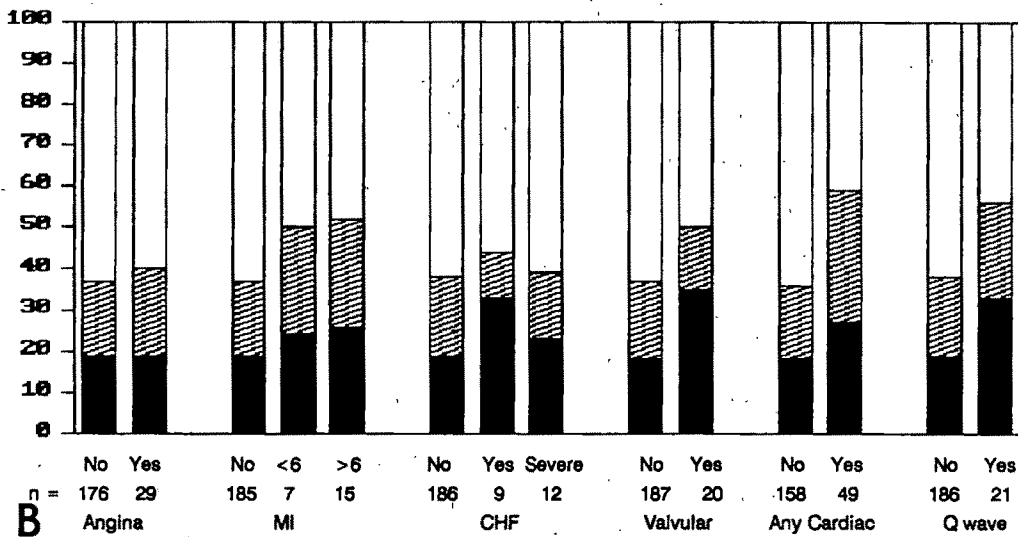
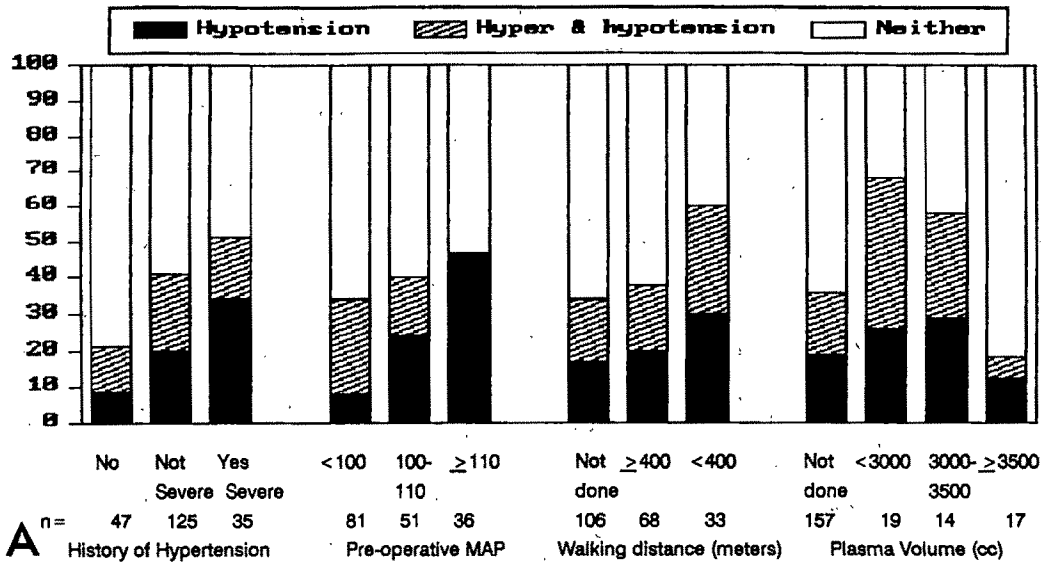
ening events (arrest, myocardial infarction, or pulmonary edema), 7 congestive failure, 17 myocardial ischemia, and 9 renal dysfunction. Thirty-four per cent of patients with intraoperative hypotension, 23% of patients with intraoperative hyper/hypotension, and 16% of those without either high-risk pattern had complications.¹¹⁻¹³ According to previous papers, patients with cardiac disease, particularly diabetics with cardiac disease, patients who had either intraoperative hypotension or hyper/hypotension, and patients who received lower net intraoperative fluids had increased rates of postoperative complications. The predictors of each specific complication varied.¹¹⁻¹³ However, for the purposes of this paper, the complication rates are shown in Table 1 according to the presence or absence of cardiac disease and diabetes, intraoperative hypotension or hyper/hypotension, and according to whether the patient had 1 or more hours during operation with a net negative fluid balance. Forty-nine per cent of the 19 diabetics with cardiac disease had complications; in contrast the 52 diabetics without cardiac disease had only 18% complications. Patients with a high-risk pattern and at least 1 hour with a negative fluid balance had especially high complication rates.

Preoperative Predictors of Patients with High-risk Hemodynamic Patterns

The purpose of the initial analysis was to test whether a history of severe hypertension, decreased functional capacity, decreased plasma volume, or the presence of cardiac disease predicted high-risk intraoperative hemodynamic patterns. Other preoperative characteristics, such as age and diabetes, were also examined to determine whether patients with either high-risk pattern differed from those without that pattern. In Figure 1 the percentage of patients who had intraoperative hypotension according

TABLE 1. Rates of Postoperative Complications: Congestive Failure, Myocardial Infarction and Ischemia, and Renal Dysfunction According to the Significant Predictors

	Neither High-risk Pattern			Intraoperative Hypotension or Hyper/hypotension		
	Intraoperative Hourly Fluid Balance			Intraoperative Hourly Fluid Balance		
	Positive	Negative	Total	Positive	Negative	Total
No cardiac disease						
No diabetes	10% (50)	15% (13)	11% (63)	10% (30)	53% (13)	23% (43)
Diabetes	19% (32)	25% (4)	19% (36)	26% (15)	0% (1)	25% (16)
Total	13% (82)	18% (17)	14% (99)	16% (45)	50% (14)	24% (59)
Cardiac disease						
No diabetes	7% (14)	0% (3)	6% (17)	40% (10)	67% (3)	46% (13)
Diabetes	55% (11)	—	55% (11)	43% (7)	100% (1)	38% (8)
Total	28% (25)	0% (3)	25% (28)	41% (17)	75% (4)	47% (21)
Model $X^2 = 16.2$ $p < .0003$; $R = 0.196$				High-risk pattern	0.71 ± 0.36	$p = 0.04$
Cardiac disease	0.82 ± 0.38	$p = 0.03$		Negative balance	0.92 ± 0.43	$p = 0.03$
Diabetes	0.82 ± 0.37	$p = 0.03$				



FIGS. 1A-C. Percentage of patients with intraoperative hypotension, hyper/hypotension, or neither high-risk pattern according to preoperative characteristics.

to their preoperative characteristics is shaded black, the percentage with hyper/hypotension is cross-hatched, and the percentage with neither pattern is white. First we will discuss the predictors of intraoperative hypotension, and second, intraoperative hyper/hypotension.

Predictors of intraoperative hypotension. As shown in Figure 1A, patients with a history of severe hypertension and those with a preoperative MAP ≥ 110 mmHg had increased intraoperative hypotension. When these two characteristics were evaluated simultaneously, the actual preoperative MAP played the important role. For example, among patients who had a history of severe hypertension but whose preoperative MAP was less than 100 mmHg, only 8% developed prolonged intraoperative hypotension; however 62% of those whose preoperative MAP was ≥ 110 mmHg had intraoperative hypotension, regardless of the previous severity. Thirty per cent of patients with a 12-minute walking distance of less than 400 m had intraoperative hypotension *versus* 21% of patients with walking distances ≥ 400 m and 18% of patients who did not have a walking distance test performed. Only 6 of the 33 patients with a walking distance of less than 400 m had any cardiac disease, so that the relationship between decreased walking distance and intraoperative hypotension was independent of their history of cardiac comorbidity. Plasma volumes were measured in 50 patients; 26% of the 19 patients with a plasma volume less than 3000 cc had intraoperative hypotension, 29% of the 14 patients with a plasma volume ≥ 3000 and less than 3500 cc, but only 12% of the 30 patients with a plasma volume ≥ 3500 cc.

As shown in Figure 1B, patients with cardiac comorbidity other than angina had slightly increased rates of intraoperative hypotension. In total 27% of patients with congestive failure, previous myocardial infarction, or valvular heart disease had intraoperative hypotension *versus* 18% of those without. Once other cardiac comorbidity was taken into account, a Q wave on ECG was not an independent predictor; only 13% of patients with a Q wave but without a history of other cardiac comorbidity had intraoperative hypotension.

There were no differences according to age or sex. Diabetics were slightly but not significantly more likely to have hypotension. Hypotension rates did not differ according to cardiac risk class or for patients with chronic pulmonary disease. Patients with chronic renal disease and those with cardiomegaly did have higher hypotension rates; however, once the preoperative MAP was taken into account, neither of these characteristics independently increased the risk of hypotension.

Multivariate analysis confirmed that the preoperative MAP, especially when ≥ 110 mmHg, and a walking distance of less than 400 m, were significant predictors of intraoperative hypotension ($p < 0.0001$ and $p = 0.044$,

respectively.) Patients with cardiac disease had slightly but not significantly increased rates. None of the other variables shown in Figure 1 were significant predictors. When logistic regression was repeated in the subset of 50 patients for whom plasma volume was available, using preoperative MAP and a walking distance of less than 400 m as covariates, decreased plasma volume achieved significance as a predictor of intraoperative hypotension ($p = 0.01$).

Predictors of intraoperative hyper/hypotension. As shown in Figure 1A, intraoperative hyper/hypotension was not more common among patients with a history of severe hypertension or among patients with high preoperative MAPs. Patients with walking distances of less than 400 m had an increased risk of intraoperative hyper/hypotension: 30% of patients with a walking distance of less than 400 m had hyper/hypotension as opposed to 16% of those without. In addition intraoperative hyper/hypotension occurred in 42% of the 19 patients with a plasma volume less than 3000 cc, in 29% of those with a plasma volume ≥ 3000 and less than 3500 cc, and in only 6% of patients with a plasma volume ≥ 3500 cc.

Intraoperative hyper/hypotension was slightly increased with the presence of cardiac disease (Figure 1B). Patients older than 70 years were more likely to have hyper/hypotension (Figure 1C). The presence of diabetes, pulmonary disease, renal disease, or cardiomegaly did not increase the risk of hyper/hypotension.

Multivariate analysis revealed that age of more than 70 years ($p < 0.006$) was the most important predictor of hyper/hypotension; walking distance less than 400 m did not achieve significance ($p = 0.08$). None of the other variables in Figure 1 were significant predictors. When the logistic regression was repeated in the 50 patients for whom plasma volume was available, using age and a walking distance of less than 400 m as covariates, decreased plasma volume again achieved significance as a predictor of intraoperative hypotension ($p = 0.03$).

Preoperative predictors of high-risk patterns. Patients with decreased functional capacity (as measured by a 12-minute walking distance of less than 400 m) were at increased risk for intraoperative hypotension and hyper/hypotension. In the 50 patients in whom it was measured, decreased plasma volume was associated with increased intraoperative hypotension and hyper/hypotension. Therefore these two hypotheses were confirmed. Cardiac comorbidity did not attain significance in the multivariable models. It was initially hypothesized that intraoperative hypertension would be most common among patients with severe hypertension; however this was not true. Instead patients with MAPs more than 110 had a significantly increased rate of hypotension. In addition age of more than 70 years was the most important predictor of hyper/hypotension.

TABLE 2. Percentage of Patients with Intraoperative High-risk Patterns (Hypotension and Hyper/hypotension) According to Plasma Volume and the Use of Diuretics

Diuretics	Plasma Volume			Total
	<3000 cc	≥3000–<3500 cc	≥3500 cc	
None	75% (8)	33% (6)	25% (12)	42% (26)
Yes	63% (11)	71% (7)	16% (6)	54% (24)
Total	68% (19)	46% (13)	22% (18)	46% (50)

Once these characteristics were considered, preoperative administration of different pharmacologic agents (*i.e.*, diuretics, beta adrenergic blocking agents, calcium channel blockers, other antihypertensive drugs, digitalis) did not affect the rates of occurrence of either high-risk pattern. Because diuretics decrease plasma volume, it was somewhat surprising that the use of diuretics was not associated with a significant increase in high-risk patterns. Table 2 shows the rates of intraoperative high-risk patterns among the 50 patients who had plasma volume measured according to the plasma volume and the use of diuretics. Fifty-eight per cent (11 of 19) of the patients with a plasma volume less than 3000 cc, 54% (7 of 13) of those with a plasma volume between 3000 and 3500 cc, but only 33% (6 of 18) of those with a plasma volume ≥3500 cc were on diuretics. Thus the use of diuretics was correlated with a lower plasma volume. However, as shown in Table 2, it was the plasma volume that was the principal predictor of high-risk patterns. Patients on diuretics with a higher plasma volume did not experience the pattern; patients not on diuretics with a lower plasma volume did.

Relationship of preoperative characteristics that predict high-risk intraoperative patterns to postoperative complications. Table 3 shows that the preoperative characteristics that predicted intraoperative hypotension or hyper/hypotension did not directly predict cardiac and renal complication rates. Complications occurred at increased rates among patients who had either high-risk pattern. Decreased functional capacity (according to a walking distance of less than 400 m), decreased plasma volume, preoperative MAP, and age define the characteristics of patients who are susceptible to particular high-risk intraoperative patterns, but patients with those preoperative characteristics who do not have intraoperative hypotension or hyper/hypotension are not at increased risk of postoperative complications.

Clearly, in addition to these preoperative characteristics, the type of operation and the expected duration of surgery must be considered when evaluating the issue of high-risk intraoperative hemodynamic patterns.

The Type and Duration of Surgery and the Risk of Hypotension and Hyper/hypotension

As shown in Figure 2, 76% of patients undergoing abdominal aortic aneurysm (AAA) repair had a high-risk

pattern as compared to 42% of those having abdominal surgery and 32% of those having vascular surgery. Only 18% of those having other types of surgery had either high-risk pattern.

Furthermore the occurrence of either high-risk patterns was directly related to the duration of surgery, with such hemodynamic changes being infrequent when surgery lasted less than 2 hours, and more common when surgery lasted more than 4 hours. However high-risk patterns were no more frequent if the duration of the operation exceeded the expected duration.

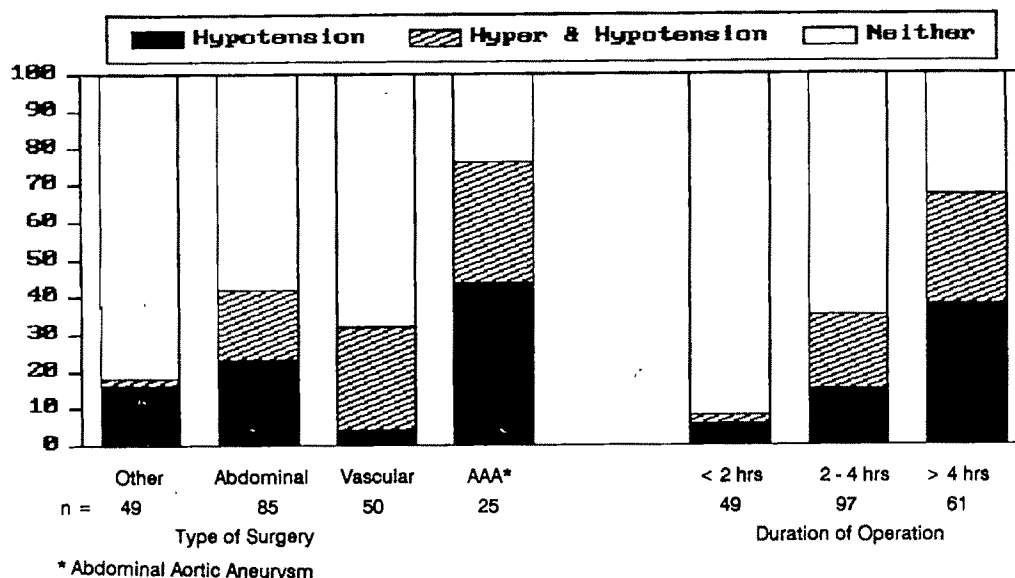
Multivariate analysis showed that, in addition to the previously identified preoperative characteristics, a duration of surgery more than 2 hours ($p < 0.0001$) or AAA repair ($p = 0.03$) were significant predictors of intraoperative hypotension, while a surgical procedure other than abdominal or vascular surgery was inversely related to intraoperative hypotension ($p = 0.02$). Similarly, in addition to the preoperative characteristics, a duration of surgery more than 2 hours ($p = 0.02$) was a significant predictor of intraoperative hyper/hypotension, while a surgical procedure other than vascular, abdominal or aortic surgery ($p = 0.03$) was inversely related to the risk.

The distribution of adverse intraoperative hemodynamic patterns according to the significant predictors (age more than 70 years, decreased functional capacity, and the type and duration of operation) are shown in Figure 3. Plasma volume was not included because data was only available for 50 patients. In this figure patients whose walking distance was less than 400 m, regardless of age, are grouped together. Patients whose surgery lasted less than 2 hours and those undergoing surgery other than vascular, aneurysm, or abdominal surgery were combined into a lower risk group (Figure 3B); patients who had more than 2 hours of abdominal, vascular, or aortic

TABLE 3. Percentage of Patients with Postoperative Cardiac and Renal Complications According to Preoperative Predictors of High-risk Intraoperative Patterns

Preoperative Characteristics	Intraoperative Pattern		
	Neither	Hypotension or Hypertension	Total
Age			
<70	12% (92)	28% (49)	18% (131)
≥70	26% (35)	29% (31)	27% (66)
Walking distance			
≥400	14% (42)	23% (26)	17% (68)
<400	8% (13)	30% (20)	21% (33)
Not done	19% (72)	32% (34)	24% (106)
Preoperative MAP			
<100	18% (72)	32% (37)	25% (109)
≥100–<110	16% (36)	23% (26)	19% (62)
≥110	11% (19)	29% (17)	19% (36)
Plasma Volume			
Not done	16% (101)	32% (56)	22% (157)
≤3500	16% (12)	20% (20)	19% (32)
>3500	21% (14)	25% (4)	22% (18)

FIG. 2. Percentage of patients with intraoperative hypotension, hyper/hypotension, or neither high-risk pattern according to type and duration of operation.



aneurysm surgery were the high-risk group (Figure 3A). High-risk patterns were more frequent when surgery was more than 2 hours and the operation was intra-abdominal, vascular, or aneurysm repair. Within that group, however, the patients who had decreased walking distances or preoperative MAPs ≥ 110 had increased rates of high-risk patterns.

Having identified the preoperative characteristics of the patients who were at risk for one of the high-risk patterns, we then examined the intraoperative course of those with the high-risk patterns *versus* those without to understand the qualitative context in which these patterns occurred. We divided the analysis into two periods: from the onset of anesthesia to the beginning of surgery (including induction and intubation) and the period of surgery itself.

Intraoperative Course at the Onset of Anesthesia: Patients with Hypotension or Hyper/hypotension Versus Those Without

In this section we evaluated how intraoperative management differed between those with and without high-risk patterns according to premedications, agents used for induction and intubation, and according to the hemodynamic patterns at the beginning of anesthesia.

Premedications. Eighty per cent of patients received atropine and nembutal, while only 5% received neither. There were no differences in the occurrence of either high-risk pattern according to the use of one or more of these premedications. Meperidine was given to 21 patients, who did not have an excess of either pattern. On the other hand, intravenous valium was given to 16 patients, 31% (5 of 16) of whom developed prolonged hypotension *versus* 19% (36 of 191) without, but this did not achieve statistical significance.

Induction and Intubation

The vast majority of patients received thiopental ($n = 186$), innovar ($n = 172$), and nitrous oxide ($n = 200$) for induction of anesthesia. There were no differences in hemodynamic patterns according to the agents used for induction; however, because most patients received similar combinations of agents, differences would not be anticipated.

A number of different neuromuscular blocking agents were used before intubation. Pancuronium alone ($n = 16$), pancuronium and succinylcholine ($n = 29$), pancuronium and D-tubocurarine ($n = 4$), D-tubocurarine alone ($n = 11$), D-tubocurarine and succinylcholine ($n = 28$), atracurium alone ($n = 13$), and atracurium and succinylcholine ($n = 5$) were all used. Succinylcholine alone was used in 72 patients and 29 patients received no neuromuscular blocking agent. There were no differences in the hemodynamic patterns according to the neuromuscular blocking agents used for induction.

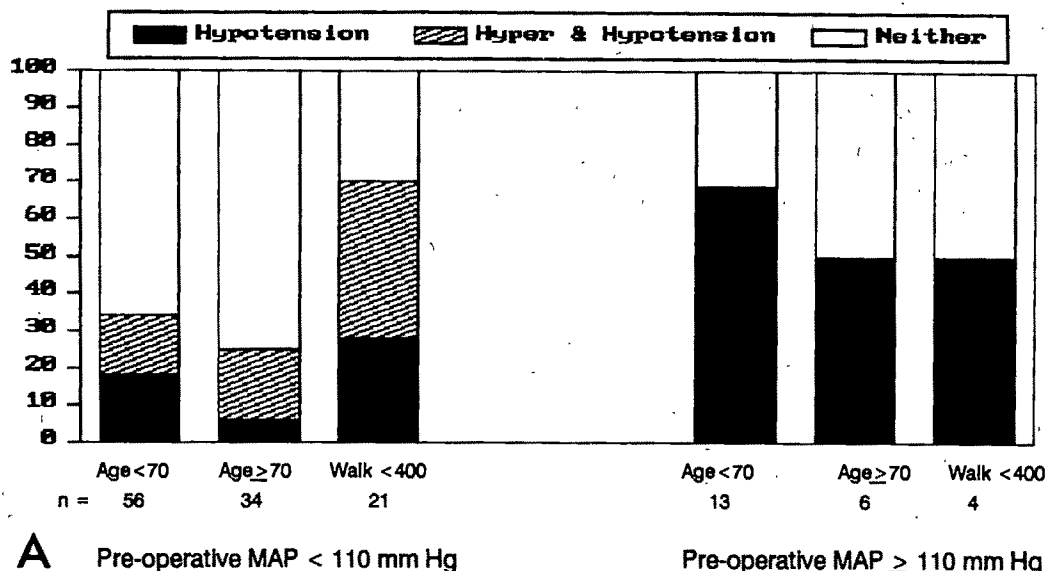
Inhalation Anesthetic Agent

There were no significance differences according to the inhalation anesthetic in the occurrence of high-risk patterns; however the majority of patients received either enflurane or isoflurane. The seven patients who received halothane were slightly more likely to have hypotension or hyper/hypotension, but this was not significant. Only one patient received methoxyflurane and 10 patients received nitrous oxide and fentanyl (none of these patients had either high-risk pattern).

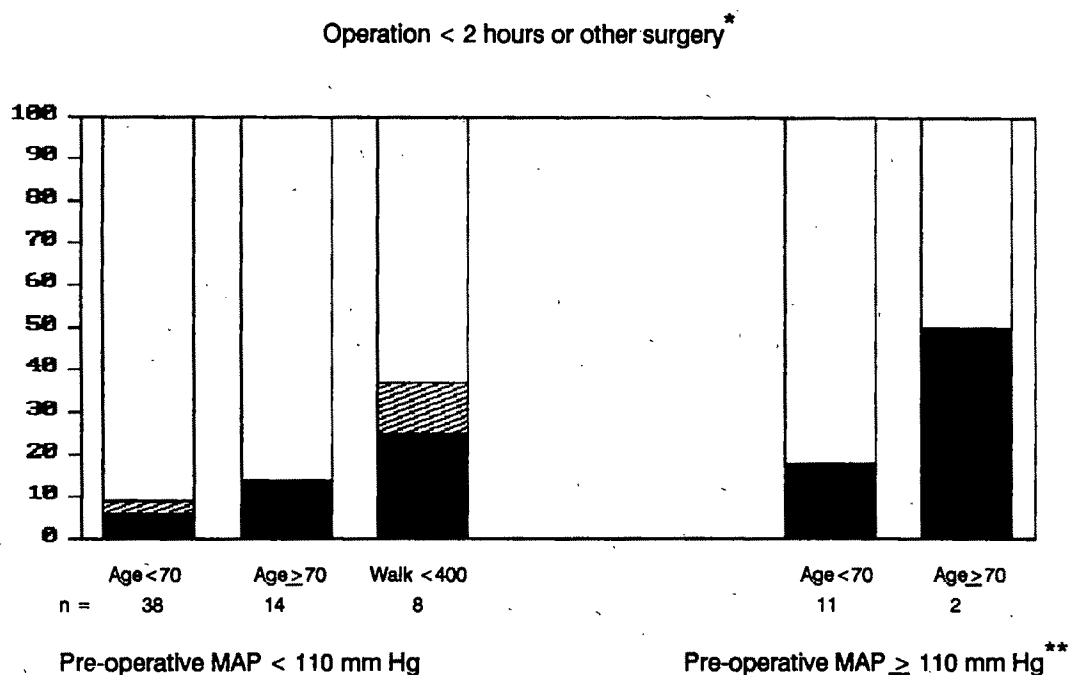
Hemodynamic Pattern during Induction and Intubation

Shown in Table 4A are the differences between the preoperative and intraoperative MAPs observed in the dif-

Operation > 2 hours and Intra-abdominal, vascular or aneurysm surgery



FIGS. 3A and B. Percentage of patients with intraoperative hypotension, hyper/hypotension, or neither high-risk pattern according to pre-operative MAP, type, and duration of operation.



* Other surgery includes all operations other than intra-abdominal vascular or aneurysm
 B** No patients with walking distance < 400 in this group

ferent hemodynamic groups immediately before induction, after induction, after intubation, and after 5 and 10 minutes of anesthesia. Patients without either of the high-risk patterns had a slight increase in MAP before induction, returned to preoperative levels after induction, had a modest increase in MAP after intubation, and then experienced a 10 mmHg decrease in MAP after 10 minutes

of anesthesia. In contrast patients who had hyper/hypotension tended to be hypertensive when they arrived in the operating room, became markedly hypertensive after intubation, and only experienced a decrease in MAP after 10 minutes of anesthesia. Patients who developed intraoperative hypotension tended to have a decrease in MAP after induction, had MAPs that remained low after in-

TABLE 4. *Changes in MAP During Induction, Intubation, and at the Onset of Anesthesia in Relation to Subsequent Hemodynamic Pattern*

	Intraoperative Hemodynamic Pattern			
	Neither (n = 127)	Intraoperative Hyper/hypotension (n = 39)	Intraoperative Hypotension (n = 41)	
A. Within patient differences in MAP (Intra-operative minus preoperatives)				
Before induction	9.3 ± 13.2	16.7 ± 12.9	3.6 ± 17.9	
After induction	2.6 ± 16.9	5.4 ± 15.7	-9.4 ± 19.0	
After intubation	8.7 ± 22.2	24.5 ± 20.6	-1.5 ± 21.6	
After inhalation				
5 minutes	-6.0 ± 17.8	3.2 ± 23.0	-15.6 ± 15.8	
10 minutes	-10.0 ± 16.4	-12.8 ± 11.9	-23.8 ± 14.8	
B. Percentage of Patients with Specific Hemodynamic Patterns				
MAP During Induction, Intubation, and First 5 Minutes of Anesthesia	Neither (n = 127)	Hyper/hypotension (n = 39)	Hypotension (n = 41)	Total (n = 207)
≥10 min ≥20 mm increase in MAP	32% (10)	56% (18)	12% (4)	100% (32)
≥10 min ≥20 mm decrease in MAP	62% (18)	—	38% (11)	100% (29)
Neither	68% (99)	14% (21)	17% (26)	100% (146)

tubation, and more of them developed a pronounced decrease after the beginning of anesthesia.

In Table 4B, patients were stratified according to changes in their MAPs during the sequence of induction and intubation; patients are divided into three groups: those who had ≥10 minutes of ≥20 mmHg increases in their MAPs, those who had ≥10 minutes of ≥20 mmHg decreases in their MAPs, and those who had neither. Of the 32 patients with ≥10 minutes of increased MAP, 56% developed the pattern of intraoperative hyper/hypotension *versus* 14% of patients without ($\chi^2 = 35$; $p < 0.001$); the sensitivity for subsequent hyper/hypotension was 27%, the specificity was 89%. Of the 29 patients with ≥10 minutes of decreased MAP, 38% developed prolonged hypotension in contrast to 17% of those without initial hypotension. ($\chi^2 = 6.9$; $p < 0.01$); the sensitivity for subsequent intraoperative hypotension was 62% and the specificity was 88%. One patient had hypertension only during induction/intubation and two patients had hypotension only during induction/intubation. Excluding these three patients from the group defined as having adverse intraoperative hemodynamic fluctuations does not change the results. Specifically the fluctuations in MAP that occurred during surgery were often heralded by the events accompanying the sequence of induction, intubation, and the onset of anesthesia; this was especially true if the patient was immediately hypotensive. Having evaluated whether the patterns differed during the period from the beginning of anesthesia to surgery, we analyzed what happened during surgery itself.

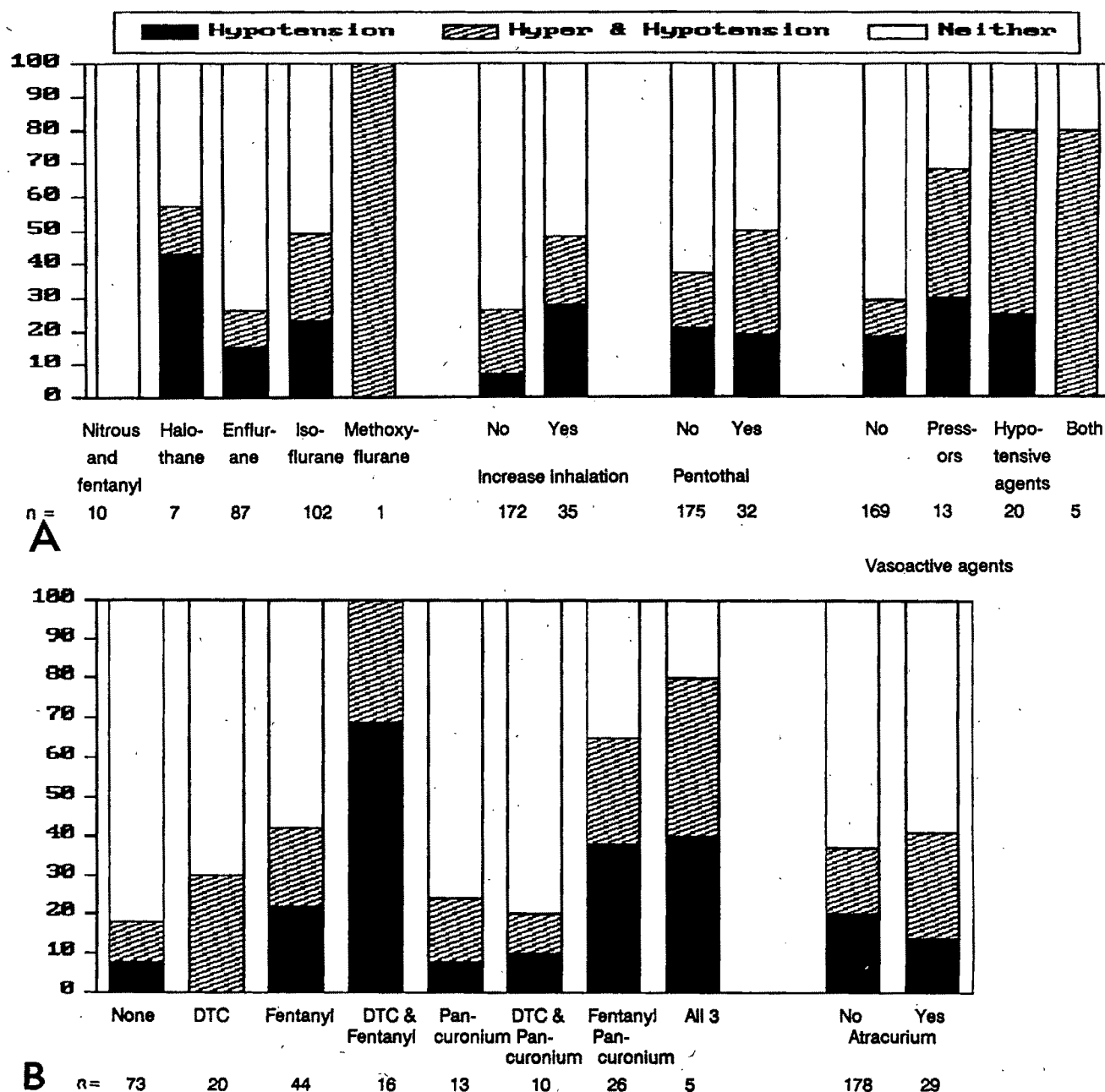
Hemodynamic Patterns During Surgery

Course of patients with intraoperative hypotension. Detailed evaluation of the 41 patients with intraoperative

hypotension as the predominant hemodynamic pattern revealed that only 21% of the patients experienced a 5- to 10-minute episode of an increase in MAP above preoperative levels at any time during operation, usually with incision or manipulation.

As expect hypotension was higher when the inhalation anesthetic was increased (Figure 4). Vasoactive drugs were used infrequently and generally only when the absolute MAP decreased to less than 70 mmHg (Fig. 4A). For example pressors were given to only four of the patients in the hypotension group, while hypotensive drugs were given to only five of the patients in this group.

Six of the 41 patients in the hypotension group experienced a decrease in MAP at the onset of anesthesia and continued to have low MAP throughout the operation. In the other 35 patients, when their MAPs increased to values similar to their preoperative MAPs, they were given either fentanyl alone, fentanyl and D-turbocurarine, fentanyl and pancuronium, pancuronium alone, D-turbocurarine, or all three. Consequently each of these agents were associated with intraoperative hypotension. For example 31% of the patients who received pancuronium *versus* 16% without pancuronium had intraoperative hypotension. Twenty-five per cent of those who received D-turbocurarine *versus* 17% without this agent had hypotension. Thirty-seven per cent of those who received more than 2 cc of fentanyl (excluding those receiving nitrous oxide-fentanyl for anesthesia) had hypotension *versus* 12% of those without it. Figure 4B shows the rates of hypotension among patients receiving combinations of these agents. Of the 47 patients who received fentanyl and a neuromuscular blocking agent, 49% had hypotension *versus* 11% of the 160 patients without agents. The use of fentanyl and neuromuscular blocking agents was partic-



FIGS. 4A and B. Percentage of patients with intraoperative hypotension, hyper/hypotension, or neither high-risk pattern according to inhalation anesthetic, the use of neuromuscular blocking agents, narcotics, and vasoactive agents during surgery.

ularly correlated with prolonged hypotension; transient increases in the pulse of more than 20 beats sometimes accompanied the subsequent decrease in MAP. In contrast prolonged hypotension did not occur more frequently among patients who received atracurium.

The anesthesiologist was apparently actively intervening when the patient's intraoperative MAP value increased and approached their preoperative MAP value. The patients were being actively maintained at levels 20 mmHg below their preoperative MAP. This is more readily un-

derstood when it is remembered that many of these patients had preoperative MAPs ≥ 110 .

Course of Patients with Intraoperative Hyper/hypotension

Detailed evaluation of patients who had intraoperative hyper/hypotension revealed that nearly one half of the patients had elevated MAPs during induction and intubation, and then the MAPs decreased. However, as shown in Table 5, the changes in MAP were not limited to those

TABLE 5. *The Patients with Intraoperative Hyper/hypotension: Changes in MAP of ≥ 20 mmHg that Occurred After the Onset of Surgery (e.g., After the Incision)*

Duration of Increased in Intraoperative MAP	Duration of Decreased Intraoperative MAP				Total
	None	5–14 min.	15–29 min.	>30 min.	
None	0	1	0	0	1
5–14 minutes	1	3	1	2	7
15–29 minutes	1	9	10	1	21
≥ 30 minutes	0	10	1	0	11
Total	2	23	12	3	39

occurring during the first minutes of anesthesia. Most of the patients had repeated episodes of intraoperative hypertension. Only those patients with ≥ 20 mmHg increases and decreases in MAP during surgery are shown in Table 5. After their intraoperative MAPs increased during surgery, many of these patients were given fentanyl and/or a neuromuscular blocking agent. For example 27% of the patients who received pancuronium *versus* 16% without had intraoperative hyper/hypotension. Twenty-eight per cent of those who received D-turbocurarine *versus* 16% without had hyper/hypotension. Twenty-nine per cent of those who received more than 2 cc of fentanyl (excluding those receiving nitrous oxide-fentanyl for anesthesia) had hyper/hypotension *versus* 17% of those without this agent.

After a neuromuscular blocking drug and fentanyl, the MAP often decreased. In total 44% of the 47 patients who were given fentanyl and a neuromuscular blocking agent had the pattern of hyper/hypotension (*versus* 11% who did not receive both of these agents). This pattern did not occur among patients who received atracurium. Not surprisingly, given the changes in MAP, vasoactive drugs were used most commonly in this group: 5 patients received pressors, 11 hypotensive agents, and 5 received both. Thirty-one per cent of these patients also received thio-pental, presumably to assess whether the hypertension was the result of light anesthesia.

The group without either high-risk pattern had either hypertension and hypotension of a shorter duration, but not both. This group tended to receive either fentanyl or neuromuscular blocking drugs for elevated MAPs but not both. Only nine received vasoactive agents. Having evaluated the anesthetic agents that were given during surgery, we also analyzed the intraoperative course in relation to fluid management.

Fluid Management

There were no important differences in the hourly net fluids (total input – total output), in the hourly net saline-containing fluids, or in the hourly blood loss between the groups (Table 6). Patients with hypotension and hyper/hypotension had higher mean central venous pressures than those without. Apart from the mean overall fluid

balance, the number of hours in which a patient had a negative fluid balance was also evaluated. For example a patient may have had a positive fluid balance at the end of the operation but may have had 1 or more hours of a negative fluid balance during the operation. When this was examined, 47% of the 38 patients who had a negative fluid balance for 1 hour or more had a high-risk pattern, in contrast to 36% of those without any hourly negative balances ($p > 0.05$).

Discussion

Underlying the study are two basic assumptions: first that preoperative characteristics influence the susceptibility to different intraoperative hemodynamic patterns; and second that intraoperative hemodynamic course relates to postoperative complications. Obviously the ability to identify patients who are likely to develop hypotension or hyper/hypotension forms the basis for preoperative and intraoperative interventions designed to prevent or ameliorate such trends.

Are Changes of 20 mmHg Too Small to Be Important?

A basic issue is how to characterize the intraoperative hemodynamic pattern. Studies have used a wide variety of strategies to define intraoperative blood pressure and pulse. In previous studies the hemodynamic patterns have been characterized as a 30% to 50% decrease or increase in systolic pressure for 10 minutes or more,^{1,4,5,8,27} as a 20% increase or decrease in MAP,⁹ or as a 20 to 50 mmHg absolute decrease in MAP.^{2,3,10} Others have evaluated

TABLE 6. *Intraoperative Hemodynamic Pattern and Intraoperative Fluid Management*

MAP	Neither (n = 127)	Intraoperative Hyper/hypotension (n = 39)	Intraoperative Hypotension (n = 41)
Total net hourly fluids	904 $\pm$ 1015	831 $\pm$ 440	801 $\pm$ 458
Net hourly saline containing fluids	770 $\pm$ 1039	689 $\pm$ 433	666 $\pm$ 410
Hourly blood loss	117 $\pm$ 289	217 $\pm$ 254	207 $\pm$ 211
CVP	7.8 $\pm$ 4.4	9.5 $\pm$ 4.4	11.3 $\pm$ 6.6

whether the systolic pressure increased to more than 180 mmHg or decreased to less than 80 mmHg; while others have evaluated whether the MAP decreased to less than 70 mmHg.^{8,28} Before this study we had selected intraoperative changes of ≥ 20 mmHg in MAP in relation to the patient's usual MAP as potentially important.

This definition was chosen because of studies of autoregulation of cerebral and renal blood flow. Normally vessels in key organs, the brain, kidneys, heart, and some viscera, vasodilate in response to decreased blood pressure and constrict in response to increased blood pressure.^{29,30} This autoregulation serves to maintain a relatively constant blood flow despite swings in systemic pressure; for example, in the normotensive, cerebral perfusion will remain normal despite fluctuations in MAP between 60 and 120 mmHg.^{29,30} When MAP decreases below the lower limit of autoregulation, hypoperfusion and ischemia occur.³¹⁻³³ When MAP increases over the upper limit of autoregulation, blood flow suddenly increases, resulting in local hyperemia.^{33,34}

In hypertensives the autoregulatory range is higher than in normotensives; in uncontrolled hypertensives, it may be 110 to 180 mmHg and in controlled hypertensives 90 to 150 mmHg.^{31,35,36} Thus in the hypertensive, the upper and lower limits for autoregulation are generally raised by 20 to 30 mmHg.³⁷ Because autoregulation in regional circulations is normally preserved within 20 to 30 mmHg of the usual MAP, we selected 20 mmHg above and below the usual MAP as the definition of important changes in intraoperative MAP. If these limits are important, then patients with ≥ 20 mm changes of longer intraoperative duration would have increased evidence of renal and cardiac complications after operation. In fact we have demonstrated in previous papers that intraoperative hypotension of 1 hour or more, or more than 15 minutes of hypertension, in combination with lesser episodes of hypertension, are significantly related to postoperative renal dysfunction, myocardial ischemia, and congestive failure.¹¹⁻¹³

It is critical to note that these definitions of hypotension and hypertension are not used in standard practice. More often absolute systolic (*i.e.*, less than 90 mmHg or more than 180 mmHg) or percentage changes in MAPs are used.^{8,38} In a previous paper we evaluated the sensitivity and specificity of different definitions of intraoperative hypotension and hypertension and found that the definitions used in this paper had the highest true-positive rate coupled with the lowest false-positive rate in predicting postoperative complications.¹⁴ Because changes of this magnitude are not customarily used to define hypotension and hypertension, it is important to note that the patients in this study were managed according to accepted standard practice.

Preoperative Predictors of Intraoperative Hemodynamics

In this study preoperative functional capacity was a significant predictor of intraoperative hypotension. Patients who were unable to walk ≥ 400 m during 12 minutes, most of whom did not have cardiac comorbidity, had increased rates of intraoperative hypotension. Initially functional capacity was assessed because measures of cardiac performance at rest are poor predictors of circulatory performance during stress, such as surgery. Most studies to date have evaluated either performance on treadmill tests^{39,40} or radionuclide cineangiograms^{41,42} as predictors of postoperative myocardial infarction or ischemia. One study found that 22% of patients who were able to achieve less than five METS on a treadmill test had postoperative ischemic complications *versus* 11% without; in addition, five of the six patients with major complications had a low exercise capacity.³⁹ Another study found a relationship between ejection fraction and ischemic complications.⁴¹ None of these studies evaluated intraoperative course in relation to preoperative exercise capacity. The present study does not provide data about the patient's ability to increment their ejection fraction in response to stress; however it is logical that patients who are unable or unwilling to walk ≥ 400 m in 12 minutes may be compromised in this regard.

Patients with a decreased plasma volume were also at increased risk of hypotension. Previous studies of trauma and shock patients have demonstrated the relationship between plasma volume and blood pressure.⁴³ Surgery results in losses of extracellular fluid.⁴⁴ Furthermore patients who were volume depleted at the time of surgery have been shown to have decreased renal plasma flow and glomerular filtration rate.⁴⁴ If extracellular fluids were immediately replaced, renal function was restored, but beyond a critical interval, the ability of the kidney to respond was lost and only circulatory overload occurred with increased fluids.⁴⁵ Therefore it is not surprising that patients with a decreased plasma volume were at increased risk for intraoperative hypotension. It should be noted also that patients older than 70 years and hypertensive patients may have decreased plasma volumes.^{46,47}

For both plasma volume and functional capacity there was missing data; it would have been preferable to have complete data on the whole population. Nonetheless the relationship between these characteristics and intraoperative hemodynamics was sufficiently strong to be statistically significant.

Postoperative complications were related to the occurrence of the intraoperative hypotension and hyper/hypotension, to the presence of cardiac disease and diabetes, were increased if net negative fluid balances occurred, and were higher among patients with cardiac disease, especially

diabetics with cardiac disease. Diabetes and cardiac disease have been identified as risk factors for postoperative cardiac complications.^{8,48} One study found that intraoperative hypotension in hypertensive patients correlated with postoperative complications but intraoperative hypertension did not.⁴⁹ In this study intraoperative hypertension correlated with postoperative complications when it was accompanied by intraoperative hypotension, rather than when it occurred alone.

Hemodynamic Response to Anesthesia and Surgery

As found in this study, induction of anesthesia with barbiturates usually results in peripheral vasodilatation, producing a 10 to 20 mmHg decrease in MAP; the decrease may be greater in volume-depleted patients or in untreated hypertensive patients with a markedly increased systemic vascular resistance.^{50,51} While fentanyl alone does not result in a decrease in pressure,⁵² the combination of fentanyl and nitrous oxide decreases cardiac output and pressure.⁵³ During intubation, normotensives have increases of 20 to 25 mmHg in MAP⁵⁴ and hypertensives may have even greater increases, possibly because they have higher norepinephrine responses to this noxious stimulus,⁵⁵ or because of the increased vascular reactivity to pressor stimuli.^{56,57} These patterns were seen in this study with a decrease in MAP after induction and an immediate increase after intubation.

After intubation all but 10 of these patients were given an inhalation anesthetic for maintenance of anesthesia (10 were maintained on a combination of nitrous-oxide and fentanyl) and the MAP decreased from postintubation levels. Halothane, enflurane, and isoflurane produce a dose-related depression of MAP,^{50,58,59} the first two from a decrease in myocardial contractility and the latter from a decrease in peripheral resistance. Myocardial blood flow decreases with halothane and enflurane; however myocardial oxygen consumption also decreases.⁶⁰

Inhalation agents alter regional autoregulation so that blood flow is more pressure dependent during anesthesia. With isoflurane, coronary blood flow is maintained, despite the decrease in systemic pressure.^{50,60} In dogs all three inhalation anesthetics impair coronary autoregulation and make flow more dependent on pressure.⁶¹ Halothane reduces cerebral metabolism and produces cerebral vasodilation at constant $p\text{CO}_2$,⁶² while isoflurane maintains cerebral autoregulation.⁶³ Renal autoregulation in the intact human may be abolished by inhalation anesthesia.³⁰ With these alterations in autoregulatory function, it is not surprising that changes in pressure were shown to correlate with postoperative cardiac and renal complications.^{27,64-67}

Changes in the intraoperative MAP can result from surgical stimulation, ventilatory changes, or anesthetic agents. Traction,⁶⁸ declamping the aorta,⁶⁹ or hypocapnia⁷⁰ may produce hypotension, while incision and clamping the aorta may produce hypertension.⁶⁹ Hypertensives may have exaggerated responses to noxious stimuli,^{71,72} resulting in greater fluctuations in MAP than in normotensives. While each of these factors may have played a role in the patterns seen in this study, there were several other trends.

In the patients who had intraoperative hypotension, as defined in this study, and who tended to have MAPs ≥ 110 before operation, the anesthesiologist often intervened with either fentanyl, D-turbocurarine, or pancuronium when the MAP started to approach (but not exceed) preoperative levels. D-turbocurarine causes reduction in MAP by reducing systemic vascular resistance,⁷³ while pancuronium may produced an increase in MAP by sympathetic stimulation and selective cardiac vagal blockade.⁷³ Thus a different target MAP was maintained during operation. For this reason the relationship between the preoperative MAP and intraoperative hypotension may be related primarily to physician management, rather than to inherent patient characteristics. Among the patients with the hyper/hypotension pattern, they began surgery with high MAPs and tended to have recurring substantial elevations of MAP, which often resulted in the administration of either fentanyl, D-turbocurarine, or pancuronium, and was followed by a substantial decrease in MAP. These patients had an intraoperative course that was extremely labile.

Patients who had a preoperative mean arterial pressure (MAP) ≥ 110 , a walking distance less than 400 m, or a plasma volume less than 3000 cc were at increased risk of intraoperative hypotension (*i.e.*, more than 1 hour of ≥ 20 mmHg decreases in the MAP). Hypotension was also more common among patients having intra-abdominal or vascular surgery, and among those who had operations lasting longer than 2 hours. Patients older 70 years or with a decreased plasma volume were at increased risk of having more than 15 minutes of intraoperative elevations of ≥ 20 mmHg over the preoperative MAP in combination with intraoperative hypotension; this was also more common when surgery lasted more than 2 hours.

Identifying patients who are susceptible to intraoperative fluctuations in MAP is only a first step. However the data may help to tailor interventions designed to prevent or ameliorate these changes or their impact.

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Suspected Myocardial Contusion

Triage and Indications for Monitoring

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Although many different tests are used to diagnose myocardial contusion, the clinical implications of the diagnosis are unclear. This makes it difficult to decide which patients require admission to a monitored bed. During 16 months, 3010 patients with blunt trauma were reviewed for evidence of sequelae attributable to myocardial contusion. None of 2204 admissions to unmonitored beds had evidence of serious arrhythmias or heart failure. No patient who died after admission had myocardial contusion at autopsy. Of the 644 admissions to monitored beds, 95 had work-ups for suspected contusion. Heart failure not obvious on admission did not occur and there were only four arrhythmias that required treatment. Conduction abnormalities on admission electrocardiogram predicted serious arrhythmias. Echocardiography and creatine phosphokinase isoenzyme levels, although frequently positive, did not predict morbidity. Clinically significant myocardial contusions are rare. Patients who will develop life-threatening complications from blunt cardiac injury can be identified in an emergency room setting.

THE REPORTED INCIDENCE of myocardial contusion after blunt chest injury ranges between 1% and 76%. Part of the reason for this wide range is the lack of a 'gold standard' test for the diagnosis.¹⁻¹⁰ Because positive test results correlate poorly with each other and there is no commonly accepted means of diagnosis, the definition of myocardial contusion has been arbitrary. A review of previous studies reveals no fewer than 14 such arbitrary definitions of myocardial contusion in the literature from the last 15 years.

Rather than concentrating on the definition of myocardial contusion, this review attempts to determine the cardiac consequence of blunt chest injury in a large number of patients. We tried to identify patients at high risk for the development of either life-threatening arrhythmias or myocardial pump failure and to develop guidelines for triage and monitoring. This issue is of more than academic

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importance. With increased regionalization of trauma care and concentration of patients in selected centers, scarce and expensive monitoring resources should be reserved for those patients with documented need.

Methods

All trauma admissions for the 16-month period beginning in September 1986 and ending in December 1987 were reviewed. Patients with penetrating injuries were excluded. A detailed review of all patients with an admission diagnosis to rule out myocardial contusion was done. Admission electrocardiogram (EKG) findings were classified as normal, sinus tachycardia, ST-T-wave changes, T-wave inversion, or conduction abnormalities. Premature ventricular contractions (PVCs), bundle branch block, supraventricular tachycardia, junctional rhythm, and first-, second-, or third-degree heart block were considered conduction abnormalities. Follow-up studies were reviewed for evidence of myocardial injury and included serum levels of creatine phosphokinase and the MB fraction of that enzyme (CPK-MB), as well as findings on echocardiography. Pericardial effusion and akinetic or dyskinetic myocardial wall motion were used to make an echocardiographic diagnosis of myocardial contusion.

All patients with suspected contusion had continuous monitoring of the EKG for 48 hours or until echocardiography was done and the results were not suggestive of myocardial contusion. All arrhythmias occurring during this period were recorded, as were any interventions made for their treatment. The cause of death was determined for all patients who died by a review of the medical records and autopsy findings.

To determine if there were patients with myocardial contusion in whom the diagnosis was missed at admission,

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the records of all patients admitted to the ward and subsequently requiring transfer to the intensive care unit were also reviewed. The reasons for their transfer, evidence for myocardial contusion, and any cardiac morbidity during their hospital stay were recorded. All coroner's autopsy reports for trauma patients who died after admission were also reviewed for any mention of myocardial contusion.

When appropriate, results are reported as means $\pm$ standard deviation.

Results

There were 3010 blunt trauma admissions during the 16-month review period (Fig. 1). Of the 101 patients declared dead in the emergency room, 14 had autopsy evidence of myocardial contusion. Another 12 had other types of cardiac injury: 7 cardiac ruptures, 3 isolated tears of the pericardium, and 2 blunt injuries to the coronary circulation. Thirteen patients died in the operating room or recovery room after emergency surgery. All of these deaths were due to uncontrollable hemorrhage or head injury. One of these patients had autopsy evidence of myocardial contusion. Ninety-five patients carried an admission diagnosis of rule-out myocardial contusion. Another two patients had blunt cardiac rupture with successful repair. The remaining 547 admissions to a monitored bed were for the treatment of other injuries. There were 47 deaths in this group, none of whom had evidence of myocardial contusion at autopsy.

There were 2252 admissions to an unmonitored bed after blunt trauma (Fig. 2). Nine of these patients subsequently required transfer to the intensive care unit, of whom two died. Most of the transfers were for respiratory distress. No patient originally admitted to an unmonitored bed and subsequently requiring transfer to the intensive care unit had any clinical evidence of myocardial contusion. Myocardial contusion was not found at autopsy in either of the two transfer patients who died.

No patient originally admitted to an unmonitored bed and not subsequently transferred to an intensive care unit bed died suddenly.

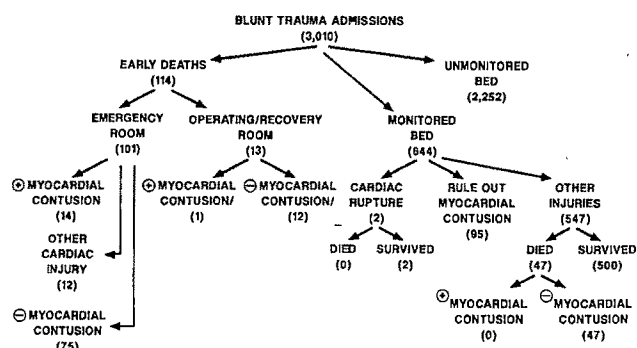


FIG. 1. Disposition of all trauma patients seen in the emergency room in the 16 months between September 1, 1986 and December 31, 1987.

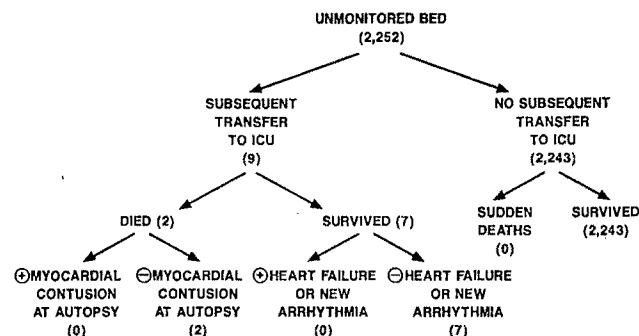


FIG. 2. Outcome and cardiac complications in patients initially admitted to an unmonitored bed.

Two patients with an admission diagnosis of rule-out myocardial contusion died (Fig. 3). Both had multiple injuries and were hemodynamically unstable on evaluation in the emergency room. Neither developed any cardiac arrhythmia within the first several days of admission and both died of multiple-organ failure. Autopsy performed on one patient determined that there was no myocardial contusion.

Other than the nonsurvivors described above, no patients with an admission diagnosis of rule-out myocardial contusion developed signs of cardiac failure. Arrhythmias occurred within 48 hours of admission in 19 (20%) patients. The relationship between admission EKG and the subsequent development of any arrhythmia and treated arrhythmias alone is shown in Table 1. In 4 of the 19 (21%) patients, the arrhythmias were considered serious enough to warrant treatment. These four cases are detailed in Table 2.

One of the four patients requiring treatment for an arrhythmia had a normal admission EKG. This was a 28-year-old motorcycle accident victim with a history of irregular heart beat. While being monitored during an orthopedic procedure 21 hours after admission, multiple unifocal PVCs with occasional bigeminy were noted. Although there were no hemodynamic consequences of the arrhythmia and the patient was asymptomatic, intravenous lidocaine was given. Cardiology consultation determined that the PVCs were a benign arrhythmia and rec-

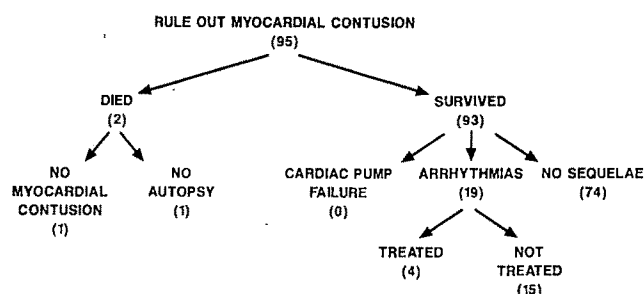


FIG. 3. Outcome and cardiac complications in patients with an admission diagnosis of myocardial contusion or rule-out myocardial contusion.

TABLE 1. Admission EKG: Relationship to Arrhythmia Development

Findings	Total Patients	Arrhythmias in First 48 Hours	Required Treatment
Admission EKG			
Normal/sinus tachycardia only	39	5	1
ST-T changes only	17	0	0
T-wave inversion only	8	0	0
Conduction abnormalities	24	13	3
Not done	7	1	0

ommended no further treatment. The patient had no evidence of cardiac dysfunction on follow-up 6 months later. The other three patients with arrhythmias requiring treatment had obvious conduction abnormalities on admission. Two of them were in their eighties and had histories of heart disease. Echocardiography was done in 93 of 95 patients (Table 3). Although echocardiography was more likely to be positive for myocardial contusion in patients who developed an arrhythmia within 48 hours of admission, it was a poor predictor of arrhythmias requiring treatment.

Different levels of CPK-MB were analyzed with respect to their ability to predict arrhythmias after admission (Table 4). Although the positive predictive value for subsequent arrhythmia increased with increasing CPK-MB values, 49% of the arrhythmias that occurred after admission were in patients with maximum CPK-MB values less than 2%. Individual values for CPK-MB in patients who had arrhythmias requiring treatment ranged between 1.2% and 9.4% (Table 2).

Discussion

Previous reviews of myocardial contusion have stressed that in any given patient no single test will always make the diagnosis and that a high index of suspicion must be maintained to ensure that subtle cases are not

TABLE 3. Echocardiography: Relationship to Arrhythmia Development

Findings	Total Patients	Arrhythmias in First 48 Hours	Required Treatment
Echocardiography			
Normal	75	11	2
Myocardial contusion	12	6	2
Nondiagnostic	6	0	0

missed.^{1,4,9,11,12} The potential for myocardial pump failure and malignant cardiac arrhythmias in patients with several negative tests for myocardial contusion also has been stressed.^{13,14} As a result of the lack of a standard diagnostic test and the spectre of life-threatening complications from undiagnosed myocardial contusion, the initial decision for a physician faced with victims of blunt thoracic trauma is not whether the patient has suffered myocardial contusion but whether the patient should be admitted to a monitored bed.

Some victims of blunt trauma with multiple injury are obvious candidates for intensive care on admission because of major multisystem injury, hemodynamic instability, or the need for mechanical ventilation. In a monitored setting, pump failure and arrhythmias can be recognized quickly and treated. High morbidity and mortality rates are seen in such patients, but the high level of associated injury makes it difficult to attribute this morbidity and mortality to the effects of myocardial contusion.^{1,4,12} Patients with lesser degrees of injury pose a more difficult triage dilemma and prompt questions such as which patients require admission to a monitored bed simply because of concern about myocardial contusion, and how long should monitoring be continued.

Of 3010 blunt trauma patients seen during a 16-month period, only one was identified who was hemodynamically stable on admission, whose admission EKG was without evidence of a conduction abnormality and who subsequently developed a potentially life-threatening arrhythmia. This patient was a young man with a history of irregular heart beat who was ultimately deemed to have a benign baseline arrhythmia. Frequent and sometimes

TABLE 2. Patients with Treated Arrhythmias

Patient	Age	Cardiac History	Admission EKG	Highest CPK-MB	Echo	Arrhythmia	Time After Admission	Treatment
C.S.	28	Irregular heartbeat	NL	2.8%	—	Multiple, unifocal PVCs, bigeminy	21 hours	Lidocaine
J.H.	17	Negative	1°–2° heart block, RBBB	3.2%	+	1°–2° heart block	Present on admission	Pacer
E.W.	80	CABG aortic valve replacement	1° heart block, RBBB	9.4%	—	Supraventricular tachycardia	48 hours	Metoprolol
F.W.	81	CABG	Multifocal PVCs	1.2%	+	Multifocal PVCs	Present on admission	Lidocaine

TABLE 4. Relationship of Highest CPK-MB in First 48 Hours and Subsequent Arrhythmias

CPK-MB (%)	Number of Patients	Any Arrhythmia	Treated Arrhythmia
<2.0	29	8	1
2.0-5.0	26	5	2
5.0-7.0	6	4	0
>7.0	4	2	1

complex ventricular ectopy is known to be present in 1% to 4% of the general population surveyed with standard electrocardiography¹⁵ and this patient probably fell into such a group. Viewed retrospectively, his arrhythmia did not require treatment.

None of the 2252 blunt trauma patients originally triaged to unmonitored beds subsequently had documented complications of myocardial contusion. This is not to say that none would have been positive if tested with radionuclide angiography, echocardiography, serial EKGs, or an arbitrarily defined level of serum CPK-MB. It is apparent, however, that even if one or several of these tests had been positive, the contusion was self-limited and there were no life-threatening clinical consequences of the missed diagnosis.

Concerns about the development of serious arrhythmias in patients with unsuspected myocardial contusion admitted to an unmonitored bed were not born out in our series. None of the patients originally admitted to an unmonitored bed and later requiring transfer to the intensive care unit had myocardial contusion either clinically or at autopsy. There were also no sudden deaths in patients admitted to an unmonitored bed.

Our low incidence of autopsy-proved myocardial contusion as compared to other series^{2,12,14,16} may reflect a lack of recognition on the part of our coroner and pathologists or their failure to vigorously search for the diagnosis. On the other hand, some of the discrepancy in rates of myocardial contusion at autopsy may have been due to our separation of patients who died in the emergency department within minutes of arrival. This group had a 14% incidence of autopsy-proved contusion in our series, which is consistent with the findings of others that myocardial contusion is an important cause of rapid death after blunt trauma.^{14,16} Our failure to find myocardial contusion at autopsy in patients who survived the immediate postinjury period emphasizes that patients with blunt cardiac injury of clinical consequence will manifest signs of their injury very quickly after trauma.

Determining the incidence of myocardial contusion in our series depends on which criteria are used to define the diagnosis (Table 5). Using the three tests most commonly applied at our institution in the diagnostic work-up of myocardial contusion, incidence ranged between

TABLE 5. Incidence of Myocardial Contusion: Relationship to Diagnostic Criteria

Diagnostic Test	Incidence (%)
Admission EKG	
Any abnormality	61
Abnormality other than sinus tachycardia or ST-T changes	43
Abnormality other than sinus tachycardia, ST-T changes, or T-wave inversion	35
Echocardiography	
Abnormal including nondiagnostic	19
Abnormal excluding nondiagnostic	14
Highest CPK-MB, first 48 hours	
>2%	55
>5%	15
>7%	6

6% if only patients with a CPK-MB level of 7% or greater were considered positive, to 61% if patients with any abnormality on their admission EKG were considered to have the diagnosis. This correlates with the incidence range found in the literature and illustrates the difficulties inherent in reporting on a disease without a sensitive and specific diagnostic test.

We found no patients with evidence of clinical sequelae of myocardial contusion who did not have hemodynamic instability on admission or a conduction abnormality on their admission EKG. Based on our review, we have simplified the triage of emergency patients with blunt trauma (Fig. 4). Patients with multisystem trauma requiring intensive care for the treatment of injuries other than possible myocardial contusion should be admitted to an intensive care unit. Pump failure and arrhythmias should be treated appropriately as they arise. The fact that we had no patients who left the ICU and subsequently suffered clinical sequelae related to myocardial contusion suggests that the decision to transfer a patient out of the intensive care unit can be made based solely on adequate treatment of other injuries and control of any cardiac dysfunction that arises during the intensive care unit stay.

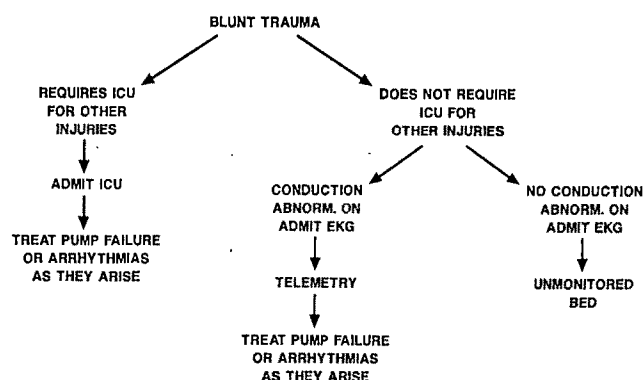


FIG. 4. Algorithm for the triage and treatment of patients with blunt trauma and suspected blunt cardiac injury.

Hemodynamically stable patients not requiring intensive care for other injuries should be triaged based on the admission EKG. Heart block, bundle branch block, PVCs, and other conduction abnormalities should prompt admission to a monitored bed for 48 hours. If no evidence of cardiac failure and no further arrhythmias occur during that interval, patients can then be transferred to an unmonitored bed. Should the original emergency room arrhythmia persist, new arrhythmias arise, or signs of cardiac failure appear, appropriate treatment should be instituted. The decision to transfer to an unmonitored bed should then be based on successful control of these problems. Echocardiography or radionuclide studies can be used to confirm the diagnosis of myocardial contusion, but these tests do not correlate well with the development of clinically significant sequelae. Echocardiographic studies may prove useful in the detection of the rare instances in which blunt thoracic injury leads to valvular disruption or ventricular aneurysm^{14,17,18} and should be done when a new cardiac murmur or evidence of pump failure develops. Serum CPK-MB levels are not useful and should not be done.

Blunt cardiac trauma should be managed based on an evaluation of associated clinical sequelae. The risk of significant morbidity from myocardial contusion in stable patients without conduction abnormalities at admission is minimal.

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Reduction of Intimal Hyperplasia and Enhanced Reactivity of Experimental Vein Bypass Grafts with Verapamil Treatment

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Recent studies have shown that calcium antagonists exert an antiatherogenic effect in animals fed cholesterol. Vein graft intimal hyperplasia is believed to be an early event in atherosclerotic lesion formation, which is a significant cause of graft failure. Altered vasoreactivity has also been postulated in the etiology of vein graft failure. Therefore this study examined the effect of verapamil treatment on the development of intimal hyperplasia and the vasoreactivity of experimental vein bypass grafts. The right external jugular vein was grafted into the right carotid artery of 30 male New Zealand white rabbits fed normal rabbit chow. The left external jugular vein was used as the control vein. Fifteen animals received verapamil (1.25 mg/day for 28 days) *via* the femoral vein by means of an osmotic pump. In 15 control animals the pump contained saline. Plasma verapamil concentration was 50.9 ± 13.2 ng/mL ($\bar{x} \pm$ SEM), a dose that showed no effect on either blood pressure, total serum cholesterol, or *in vitro* platelet aggregation to ADP. Fourteen of fifteen grafts were patent in each group, for a patency rate of 93%. Histologic examination using computer morphometry showed significant reduction of intimal hyperplasia at the proximal, middle, and distal graft segments ($p < 0.05$). In addition *in vitro* isometric tension studies of the vein grafts and control veins showed that verapamil causes enhanced reactivity of both vein grafts and control veins in response to norepinephrine and histamine ($p < 0.05$). Reactivity of vein grafts to serotonin was unaltered. While none of the normal veins in the control group responded to serotonin, normal veins treated with verapamil contracted readily in response to serotonin. Endothelial-dependent relaxation to acetylcholine was absent in both control and verapamil-treated vein grafts, while normal veins from both groups responded to the same extent to acetylcholine. Because we could not demonstrate any difference in platelet or endothelium function between untreated and verapamil-treated animals, we examined the direct effect of verapamil on smooth muscle. Verapamil significantly inhibited [^{3} H]-thymidine incorporation into DNA in vascular smooth muscle cells

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in culture in a dose-dependent manner. Verapamil treatment significantly reduces intimal hyperplasia in experimental vein grafts and inhibits smooth muscle cell proliferation in culture. Furthermore the enhanced reactivity to norepinephrine and histamine in the verapamil-treated vessels has no detrimental effect on the patency rate at 4 weeks. Thus by inhibiting intimal hyperplasia, calcium antagonists may improve the long-term patency of vein bypass grafts.

CLINICALLY CALCIUM ANTAGONISTS are used in the treatment of a variety of cardiovascular disorders¹ and frequently are administered to patients who undergo bypass procedures. Studies on various experimental models of atherosclerosis have indicated an antiatherogenic effect of various calcium antagonists such as nifedipine,² verapamil,³ diltiazem,⁴ and lanthanum.⁵ Furthermore we⁶ and others⁷⁻⁹ have shown that treatment with calcium antagonists significantly reduces the development of intimal hyperplasia after mechanical injury of arteries. The underlying mechanism of this action is still unclear.

The reversed autogenous vein has long been the graft material of choice for treatment of occlusive vascular disease. However the reported high failure rates of 10% to 40% at 1 year¹⁰ due mainly to thrombotic events and of 50% to 60% at 10 years¹¹ due to progressive intimal hyperplasia are considered to be major clinical problems. The pathogenesis of vein graft occlusion appears to have some similarities to the development and progression of atherosclerosis. Endothelial cell injury is thought to be the precipitating event in both situations.¹² Several investigators have shown that aspirin, dipyridamole,¹³ and heparin¹⁴ reduce the development of intimal hyperplasia in vein bypass grafts.

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Although vasospasm has been reported as an etiology for vein graft failure,¹⁵ little information is available on vein graft vasomotor function. Calcium has been implicated in a number of the events involved in the etiology of vein graft failure, including aggregation of platelets, release of platelet-derived growth factor (PDGF),¹⁶ proliferation¹⁷ and migration¹⁸ of smooth muscle cells, and extracellular matrix formation.¹⁹ Therefore it is reasonable to suppose that interference with intracellular calcium concentration may have a beneficial role in reducing vein graft occlusion rate. Calcium is also involved in the production of endothelium-derived relaxing factor (EDRF) and prostacyclin,^{20,21} suggesting that the use of calcium antagonists may play a role in modulation of vascular reactivity.

In this study we examined the effect of chronic verapamil treatment on vasomotor function and the development of intimal hyperplasia in autogenous experimental vein bypass grafts. To examine other mechanisms by which verapamil may alter intimal hyperplasia, the effects of chronic verapamil treatment on total cholesterol concentration, blood pressure, *in vitro* platelet function, and DNA synthesis in smooth muscle cells in culture were also investigated.

Methods

Experimental Design

Male New Zealand white rabbits underwent autogenous vein bypass grafting of the right carotid artery using the right external jugular vein. At surgery an osmotic pump was also placed and verapamil was administered *via* the femoral vein during the next 28 days. In control animals the pump contained vehicle (saline) only. Plasma verapamil, total serum cholesterol concentration, and blood pressure were determined before and 1 and 3 weeks after initiation of therapy. *In vitro* platelet aggregation to ADP was tested in both groups. After 4 weeks the vein grafts and the left external jugular vein (control vein) were harvested. Intimal hyperplasia was measured in cross-sections of the proximal ($n = 11$), middle ($n = 13$), and distal ($n = 11$) graft segments. Segments of vein grafts ($n = 10$) and control veins ($n = 10$) were suspended in an organ bath to assess endothelial cell function and to determine the contractile responses to norepinephrine, histamine, and serotonin.

Animal Operations

Thirty male New Zealand white rabbits (weighing 2 to 2.5 kg) were used in this study. All animals were fed normal rabbit chow for the duration of the experiment. Fifteen animals received verapamil hydrochloride (dissolved in saline; Sigma Chemical Co., St. Louis, MO) at a dose of 1.25 mg/day for 28 days *via* the femoral vein by means

of an osmotic pump (the Alzet osmotic pump, model 2ML4, Alza, Palo Alto, CA). In 15 control animals the pump contained sterile saline solution.

Surgical Procedures

Anesthesia was induced with Ketamine hydrochloride (60 mg/kg, Ketaset, Aveco Co., Inc., Fort Dodge, IA), xylazine (6 mg/kg, Rompun, Mobay Corp., Shawnee, KA), and acepromazine maleate (1.5 mg/kg, PromAce, Aveco Co., Inc., Fort Dodge, IA). Antibiotic prophylaxis was provided by giving one intramuscular dose of benzathine and procaine penicillin (30,000 units/kg, Flo-cillin, Aveco Co., Inc.) at induction of anesthesia. The surgical procedures were performed using clean conditions and an operating microscope (JKH 1420, Edward Weck, Inc., Research Triangle Park, NC). Through a small longitudinal inguinal incision, the right femoral vein was dissected. An EP-60 catheter (Intramedic, polyethylene tube, Clay Adams, Parsippany, NJ) attached to the osmotic pump was inserted *via* a small transverse venotomy and fixed to the vein. The pump was placed in the subcutaneous tissue and the wound was closed. After exposure through a right longitudinal neck incision, the right external jugular vein was carefully dissected, excised, and maintained in heparinized saline (5 units/mL, Elkins-Sinn, Inc., Cherry Hill, NJ) for approximately 15 minutes while the right common carotid artery was exposed and mobilized. Heparin (200 units/kg) was administered intravenously. After proximal and distal control of the right common carotid artery, a proximal longitudinal arteriotomy was made. The reversed external jugular vein was then anastomosed to the artery in an end-to-side manner using a continuous 10-0 microvascular monofilament nylon suture (Ethilon, Ethicon, Inc., NJ). The distal anastomosis was performed in a similar manner. Care was taken throughout the procedure to avoid unnecessary instrumentation of the vein segment. The right common carotid artery was ligated and divided between the two anastomoses. The artery was then unclamped, hemostasis was obtained, and the wound was closed. Four weeks after grafting, each rabbit was anesthetized and the graft was harvested without perfusion fixation because we have previously determined that this is unnecessary for histologic examination of the grafts (unpublished data). The previously unmanipulated left external jugular vein was excised and used as a control vein for the *in vitro* isometric tension studies. Animal care complied with the *Principles of Laboratory Animal Care and the Guide for the Care and Use of Laboratory Animals* (NIH Publication No. 80-23, revised 1985).

Plasma Levels and Physiologic Effect of Verapamil

Blood samples were drawn from the ear vein for determination of plasma verapamil and total serum chole-

terol concentrations. Plasma samples for verapamil were assayed by high-pressure liquid chromatography (HPLC, Pumpsystm:LCD, Riviera Beach, FL) based on the method of Harapat.²² Verapamil was extracted in ethyl ether and after evaporation the drug residue was reconstituted in the HPLC solvent and injected onto the column (Chromanetics Corp., Kensington, MD). Verapamil was quantitated using a fluorescence detector (FS 970, Schoeffel Instruments, Westwood, NJ). Total serum cholesterol was determined by the method of Chiamori and Henry,²³ using ferric chloride and glacial acetic acid. Blood pressure was measured before and after treatment *via* the middle ear artery of the rabbit using a Millar Micro-Tip pressure transducer (Millar Instruments, Inc., Houston, TX).

In vitro platelet aggregation was tested in both groups. Citrated blood samples were collected and ADP at a concentration from 0.2 $\mu\text{mol/L}$ (micromolar) to 2.0 $\mu\text{mol/L}$ was added to platelet-rich plasma adjusted to 300,000 platelets/ μL with platelet-poor plasma.²⁴ Aggregation was measured by light transmission using a Chrono-log aggregometer (Chrono-log model 335, Havertown, PA).

In Vitro Isometric Tension Studies

Vessel rings, 4 to 5 mm in length, were cut from both the vein graft and the control vein (two rings of tissue from each vessel). The vessel rings were suspended by stainless steel hooks in an organ bath containing Krebs solution of the following millimolar composition: NaCl 122; KCl 4.7; MgCl_2 1.2; CaCl_2 2.5; NaHCO_3 15.4; KH_2PO_4 1.2; glucose 5.5, bubbled with 95% O_2 and 5% CO_2 (pH 7.4) and maintained at 37 C. One hook was fixed to the bottom of the bath and the other hook was connected to a force transducer (Myograph F-60, Narco Bio Systems, Houston, TX). Tension was recorded on a multichannel chart recorder (Physiograph MKIII-S, Narco Bio Systems, Houston, TX). The vessel rings were allowed to equilibrate at a constant tension of 0.5 g for 1 hour. During the equilibration period, the Krebs' solution in the organ bath was replaced every 30 minutes.

Cumulative addition of norepinephrine (dissolved in 10^{-3} mol/L [molar] HCl, Sigma Chemical Co.) to the organ bath resulted in sigmoid dose-response curves. After a washout and re-equilibration period of 30 minutes, endothelium-dependent relaxation was studied by adding acetylcholine (10^{-8} mol/L to 10^{-5} mol/L) to the vessel rings precontracted with the ED_{50} dose (the concentration of agonist required to elicit 50% of the maximal response) of norepinephrine.

After further washouts and re-equilibration periods, dose-response curves were obtained in response to histamine and serotonin (dissolved in distilled water; Sigma Chemical Co.). These curves were normalized in terms of the percentage of maximal contraction, and Probit

analysis (SAS, SAS Institute, Inc., Cary, NC) was used to calculate the ED_{50} value for each ring of tissue. After further washouts, normal veins from the verapamil-treated animals were incubated with phentolamine [10^{-6} mol/L] for 30 minutes and then the ED_{50} dose of serotonin was added to the organ bath.

Histologic Methods

The morphology of the control and grafted vessels from both groups was examined by light microscopy. Four weeks after surgery, the proximal, middle, and distal graft segments were excised and fixed in 10% formalin. Cross-sections were dehydrated and embedded in paraffin. Six-micron sections were cut and stained with a modified Masson's trichrome and Verhoeff's elastic tissue stain. Intimal thickening was measured by computerized videometric analysis (Innovision 100, American Innovision Inc., San Diego, CA). The average intimal thickness was calculated from 20 measurements of intimal thickness taken at even intervals around the circumference of each section.

[³H] Thymidine Incorporation in Vascular Smooth Muscle Cells

Vascular smooth muscle cells from the media of the thoracic aorta of male New Zealand white rabbits were isolated and grown in tissue culture. Cells in the 6th through 12th passage were used for these experiments. Confluent cells in 75 cm^2 culture flasks (Falcon Plastics, Lincoln Park, NJ) were washed twice with 8 mL phosphate-buffered saline (Gibco Laboratories, Grand Island, NY) followed by trypsinization for 7 minutes at 37 C with 8 mL trypsin/EDTA solution (Gibco). Three milliliters of Dulbecco's minimal essential medium (Gibco) with 10% fetal calf serum (Gibco) was then added to inactivate the trypsin. The cells were isolated by centrifugation (250g, for 10 minutes) and resuspended in Dulbecco's minimal essential medium with 10% fetal calf serum containing penicillin (100 $\mu\text{g/mL}$) (growth medium, Gibco). Culture wells (6-well cluster dishes, 35 mm diameter; Falcon Plastics) were inoculated with 2 mL growth medium containing 5×10^4 cells.

The growth medium was replaced with new medium every third day until the cells reached confluency as judged by microscopic examination. The cells grew in hills and valleys typical of vascular smooth muscle cells. On reaching confluency, the medium was not changed for 4 days. This regimen produced a quiescent state in the cells similar to that achieved by incubating the cells in minimal essential medium containing 0.1% fetal calf serum. On the day of the experiment, new growth medium was exchanged 4 hours and again 2 hours before the initiation of the experiment. The experiments were initiated by exchanging the growth medium with new medium contain-

ing 4 μCi [^3H]-thymidine (New England Nuclear, Boston MA) and various concentrations of verapamil. The concentration of verapamil used ranged from 0 to 100 $\mu\text{mol/L}$. Incorporation of [^3H]-thymidine into acid-precipitable material was measured after a 24-hour incubation period (air plus 5% CO_2 at 37 C). At harvest the dishes were placed on ice and each well was washed twice with 2 mL of ice-cold Dulbecco's phosphate-buffered saline (Gibco). Two milliliters ice-cold 5% trichloroacetic acid was added. After 5 minutes the acid was removed and each well washed with 3 mL ice-cold water. Sodium hydroxide (1 mL, 0.3N) was then added and the dishes were incubated for 10 minutes at 37 C. A 100- μL aliquot of the sodium hydroxide solution was counted in 10 mL Biofluor (New England Nuclear, Boston, MA) by a Packard Tri-Carb 4530 scintillation counter (Packard Instruments Inc., Downers Grove, IL). Results are expressed as percentage of control.

Statistics

Data processing and analysis were accomplished with a computer software program (Statgraphics, Statistical Graphics Corp., Rockville, MD). All data are expressed as the mean $\pm$ standard error of the mean. Relaxation in response to acetylcholine is expressed as the percentage of decrease in contractile tension developed to norepinephrine. Statistical comparisons of the mean values of ED_{50} for control arteries and arterial grafts were made by Student's two-tailed, paired *t* test. Differences were considered significant at $p < 0.05$.

Results

At harvest 4 weeks after surgery, all pumps were functioning, and 14 of 15 grafts were patent in each group,

TABLE 1. Effect of Verapamil on Vein Graft Intimal Thickness

Group	Intimal Hyperplasia		
	Proximal	Middle	Distal
Control	252 $\pm$ 19	154 $\pm$ 3	257 $\pm$ 1
Verapamil	195 $\pm$ 7	133 $\pm$ 9	221 $\pm$ 5
<i>p</i> value	<0.02	<0.05	<0.02

Intimal hyperplasia expressed as intimal thickness in microns (mean $\pm$ SEM). Middle segment ($n = 13$); proximal and distal segment ($n = 11$).

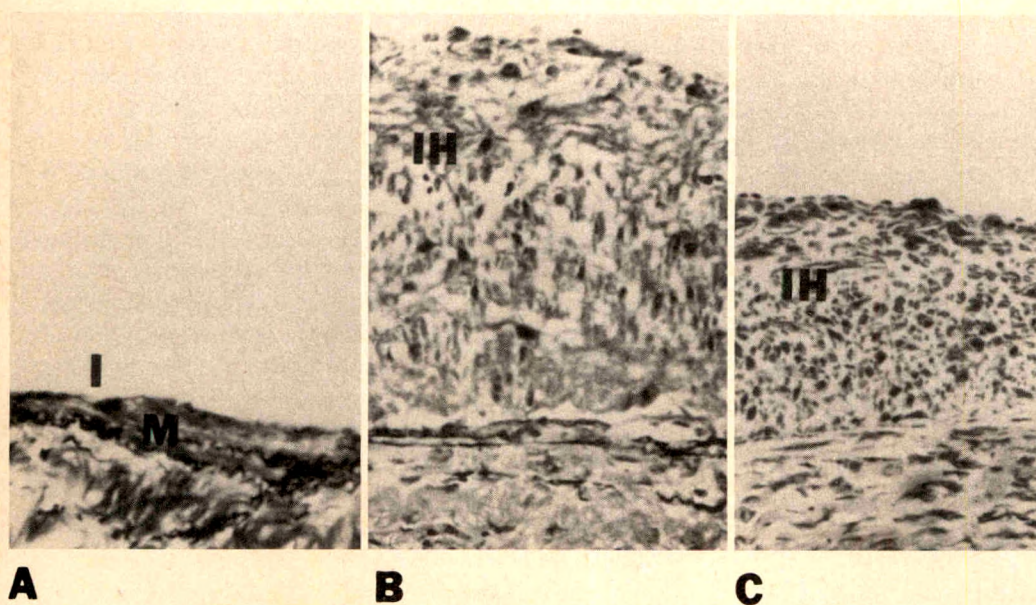
yielding a graft patency rate of 93%. The mean plasma verapamil level was 50.9 ± 13.2 ng/mL, which is within the clinically accepted therapeutic range for humans.

Histologic Results

The light microscopic appearance of normal rabbit external jugular vein demonstrated a thin-walled vessel with a single-cell layer intima, and media consisting of a few smooth muscle cells as well as collagen and elastin (Fig. 1A). There is no marked distinction between the intima and media in the rabbit normal vein. All vein grafts 4 weeks after surgery exhibited some degree of intimal hyperplasia consisting of a proliferation of smooth muscle cells and deposition of collagen and elastin (Fig. 1B and C). Morphometric determinations of intimal thickness showed a significant reduction in the amount of intimal hyperplasia in the proximal, middle, and distal segments of the verapamil-treated grafts as compared to the control vein grafts (Table 1).

Plasma Levels and Physiologic Effect of Verapamil

Verapamil treatment showed no effect on total serum cholesterol concentration (54.4 ± 3.7 mg/dL in the control



FIGS. 1A–C. Photomicrograph of a normal external jugular vein (A) demonstrating single cell layer intima (I) and a thin layer of smooth muscle cells constituting the media (M). Control (saline-treated) vein graft (B) demonstrating intimal hyperplasia 4 weeks after surgery. Verapamil-treated vein graft (C) demonstrating the reduction in intimal hyperplasia. Modified Masson's trichrome and Verhoeff's elastic tissue stain. Original magnification $\times 66$.

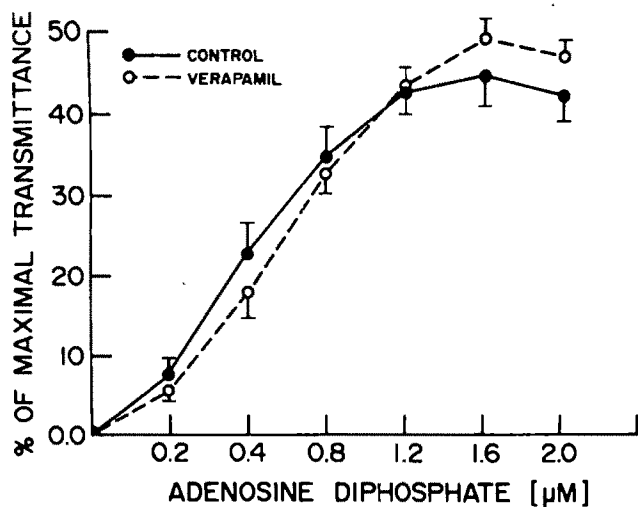


FIG. 2. Effect of verapamil on platelet aggregation induced *in vitro* by ADP (0.2 to 2.0 μ M). The results are presented as the percentage of maximal transmittance (mean $\pm$ SEM). There was no statistical difference ($p = \text{NS}$) between verapamil and control samples.

animals versus 49.9 ± 3.7 mg/dL for the verapamil-treated animals). Similarly there was no difference in blood pressure measurements between verapamil-treated animals (106.7 ± 3.1 mmHg) and control animals (108.3 ± 3.7 mmHg).

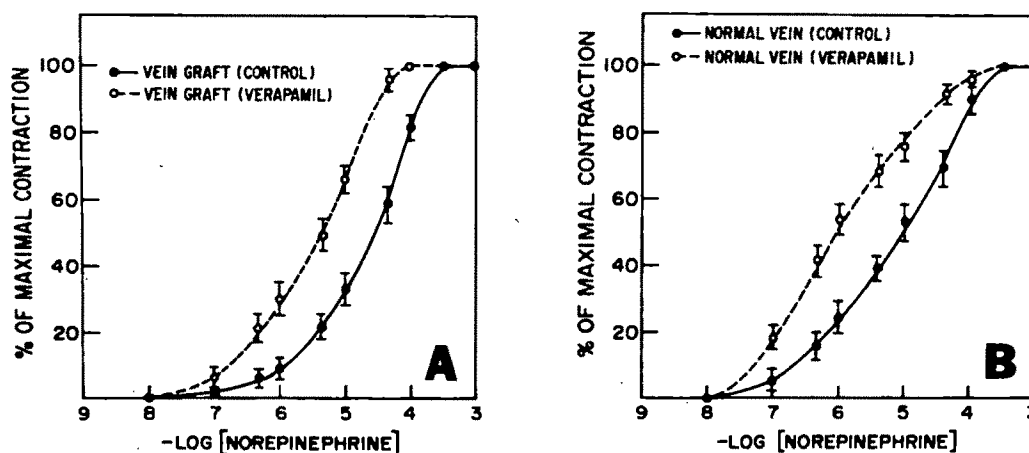
In vitro platelet aggregation in response to ADP (0.2 μ mol/L to 2.0 μ mol/L) of plasma samples from both groups are shown in Figure 2. There was no statistically significant difference in the aggregability of platelets from control and verapamil-treated animals, indicating that a plasma verapamil level of 50.9 ± 13.2 ng/mL has no significant effect on platelet aggregation.

In Vitro Isometric Tension Studies

The cumulative addition of norepinephrine to normal vein and vein graft segments in both verapamil- and saline-treated animals resulted in sigmoid dose-response curves (Fig. 3). The ED_{50} was $27.1 \pm 5.6 \times 10^{-6}$ mol/L for vein grafts from the saline-treated animals and was shifted to the left for vein graft treated with verapamil ($11.3 \pm 3.7 \times 10^{-6}$ mol/L), demonstrating that verapamil-treated vein grafts were significantly ($p < 0.05$) more sensitive to norepinephrine compared to saline-treated vein grafts (Fig. 4). Similarly the ED_{50} was $11.3 \pm 2.3 \times 10^{-6}$ mol/L for normal veins treated with saline and was shifted to the left for normal veins treated with verapamil ($2.9 \pm 0.3 \times 10^{-6}$ mol/L), demonstrating that normal veins treated with verapamil were significantly ($p < 0.05$) more sensitive to norepinephrine compared to saline-treated normal veins (Fig. 4).

The cumulative dose-response curve for verapamil-treated vein grafts to histamine was also shifted to the left (Fig. 5). The ED_{50} to histamine for saline-treated vein grafts was $32.9 \pm 9.0 \times 10^{-6}$ mol/L, and was $4.0 \pm 0.8 \times 10^{-6}$ mol/L for verapamil-treated vein grafts ($p < 0.05$) (Fig. 4). Similarly the dose-response curve for verapamil-treated normal veins to histamine was shifted to the left. The ED_{50} to histamine for saline-treated normal veins was $6.3 \pm 0.7 \times 10^{-6}$ mol/L, and was $1.7 \pm 0.3 \times 10^{-6}$ mol/L for verapamil-treated normal veins ($p < 0.05$) (Fig. 4).

In contrast the cumulative addition of serotonin produced a similar contractile response in both saline- and verapamil-treated vein grafts (Fig. 6). The ED_{50} to serotonin for saline-treated vein grafts was $1.3 \pm 0.4 \times 10^{-6}$ mol/L and for the verapamil-treated vein grafts it was 1.3



FIGS. 3A and B. (A) Dose-response curves to norepinephrine for control (saline-treated) vein grafts ($n = 10$) and verapamil-treated vein grafts ($n = 10$) at 4 weeks. Each point represents the mean $\pm$ SEM. The ED_{50} value for verapamil-treated vein grafts was significantly ($p < 0.05$) shifted to the left, demonstrating the increased sensitivity to norepinephrine. (B) Dose-response curves to norepinephrine for control (saline-treated) normal veins ($n = 10$) and verapamil-treated normal veins ($n = 10$) at 4 weeks. Each point represents the mean $\pm$ SEM. The ED_{50} value for verapamil-treated normal veins was significantly ($p < 0.05$) shifted to the left, demonstrating the increased sensitivity to norepinephrine.

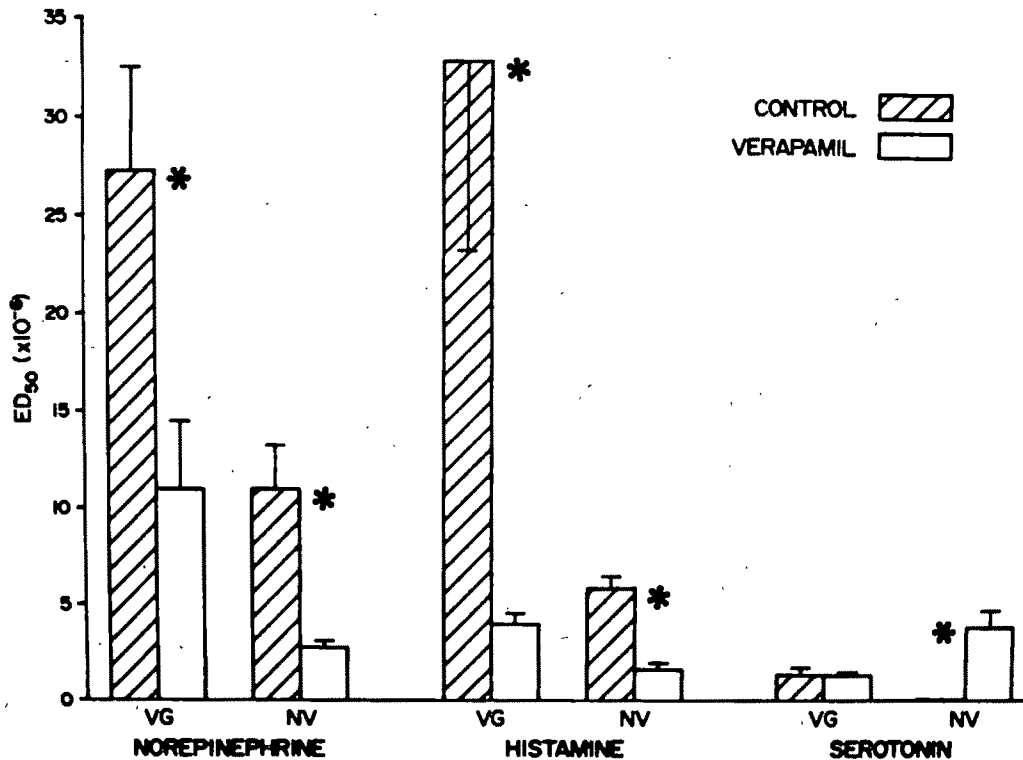


FIG. 4. Contractile response expressed as ED₅₀ of normal veins and vein grafts in the control (saline-treated) and verapamil-treated animals 4 weeks after surgery. All values are mean $\pm$ SEM (n = 10). *Signifies p < 0.05.

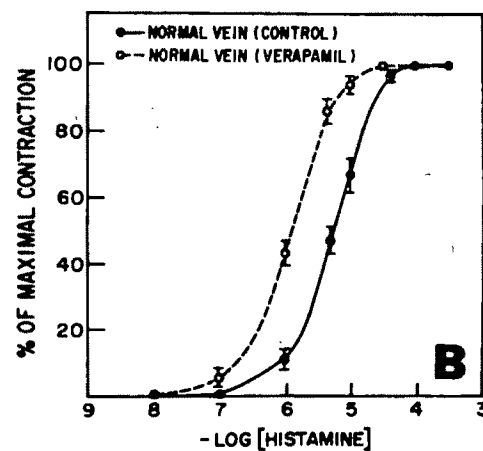
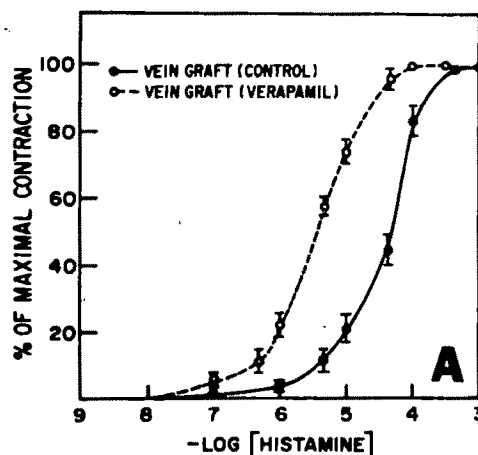
$\pm 0.2 \times 10^{-6}$ mol/L (p = NS). While none of the saline-treated normal veins contracted in response to serotonin, verapamil-treated normal veins contracted in response to serotonin, exhibiting a sigmoid dose-response curve (Fig. 6). The ED₅₀ for verapamil-treated normal veins to serotonin was $11.7 \pm 0.8 \times 10^{-6}$ mol/L (p < 0.05) (Fig. 4).

Addition of acetylcholine to vessel rings precontracted with norepinephrine was used to assess endothelial cell function. Vein grafts from all verapamil-treated animals as well as control animals demonstrated no relaxation in response to acetylcholine. This indicates that verapamil

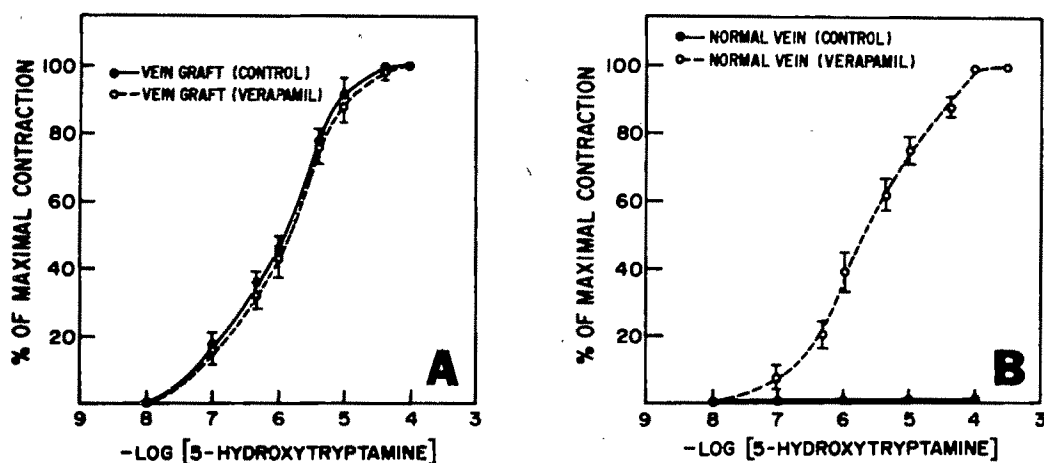
treatment has no effect in maintaining endothelial-dependent relaxation in response to acetylcholine in these grafts. However normal veins from both groups relaxed in response to acetylcholine in a dose-dependent manner, and there was no significant difference in their dose-response curves (Fig. 7).

[³H]-Thymidine Incorporation

Verapamil produced a dose-related inhibition of DNA synthesis in rabbit vascular smooth muscle cells in culture.



FIGS. 5A and B. (A) Dose-response curves to histamine for control (saline-treated) vein grafts (n = 10) and verapamil-treated vein grafts (n = 10) at 4 weeks. Each point represents the mean $\pm$ SEM. The ED₅₀ value for verapamil-treated vein grafts was significantly (p < 0.05) shifted to the left, demonstrating the increased sensitivity to histamine. (B) Dose-response curves to histamine for control (saline-treated) normal veins (n = 10) and verapamil-treated normal veins (n = 10) at 4 weeks. Each point represents the mean $\pm$ SEM. The ED₅₀ value for verapamil-treated normal veins was significantly (p < 0.05) shifted to the left, demonstrating the increased sensitivity to histamine.



FIGS. 6A and B. (A) Dose-response curves to serotonin for control (saline-treated) vein grafts ($n = 10$) and verapamil-treated vein grafts at 4 weeks. Each point represents the mean $\pm$ SEM. There was no difference between the ED_{50} values for control and experimental vein grafts ($p = NS$). (B) Dose-response curves to serotonin for control (saline-treated) normal veins ($n = 10$) and verapamil-treated normal veins at 4 weeks. Each point represents the mean $\pm$ SEM. Normal veins did not respond to serotonin while normal veins from verapamil-treated animals demonstrated a sigmoidal dose-response curve.

Verapamil at 10 $\mu\text{mol/L}$, 50 $\mu\text{mol/L}$, and 100 $\mu\text{mol/L}$ showed a significant inhibition of [^3H]-thymidine incorporation into rabbit smooth muscle cells by $19.7\% \pm 5.1\%$, $65.7\% \pm 4.3\%$, and $83.0\% \pm 3.1\%$, respectively (Fig. 8).

Discussion

In this study we have shown that verapamil treatment in experimental vein bypass grafts significantly reduces the development of intimal hyperplasia, a possible early lesion in atherosclerosis. This reduction of intimal hyperplasia was achieved at plasma levels of verapamil within the therapeutic range in humans.

Verapamil has been shown to reduce atherosclerosis. Because the cholesterol carried in low-density lipoproteins is principally involved in atherogenesis,²⁵ verapamil may

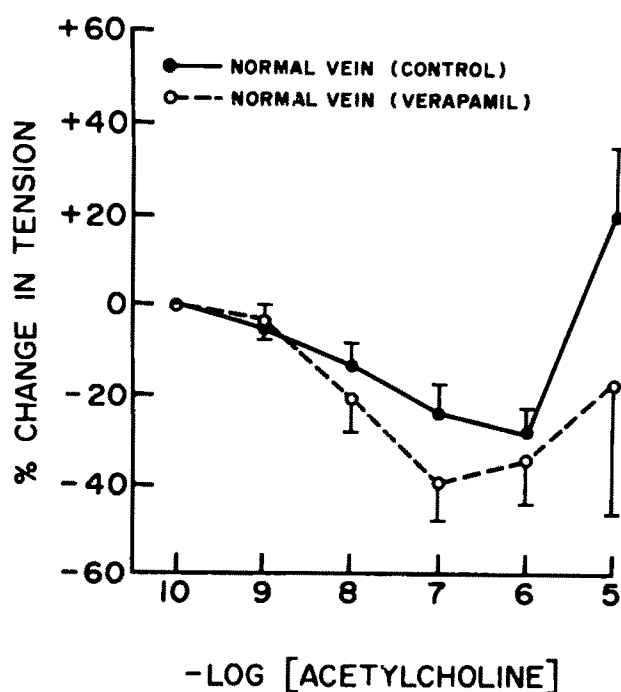


FIG. 7. Dose-response curves to acetylcholine in normal veins from verapamil-treated animals ($n = 8$) and from saline-treated animals ($n = 8$). Values are presented as percentage change in tension (mean $\pm$ SEM) from precontraction to an ED_{50} norepinephrine dose. There was no statistical difference ($p = NS$) at each point between the two groups. There was a significant relaxation induced by acetylcholine in normal veins from animals treated or untreated with verapamil.

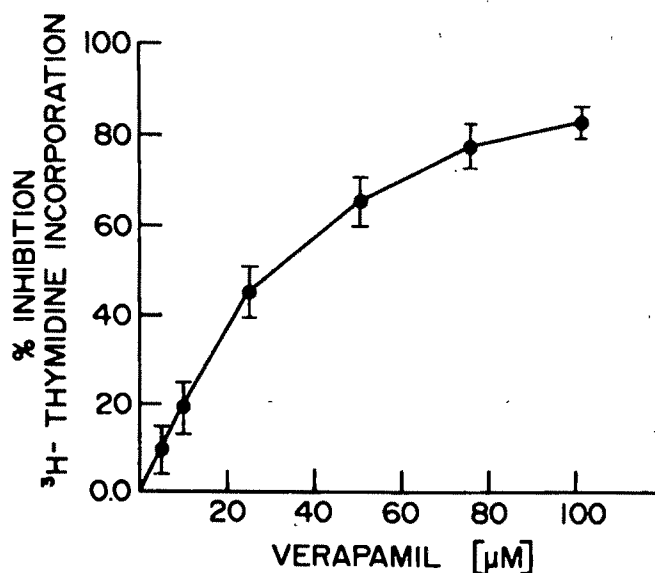


FIG. 8. The effect of verapamil on incorporation of [^3H]-thymidine into DNA of rabbit vascular smooth muscle cells in culture. Each point is the mean $\pm$ SEM.

exert its antiatherogenic activity through an effect on total plasma cholesterol levels. However this study and other previous studies have demonstrated that verapamil has no effect on either the concentration of total serum cholesterol or the concentration of low-, very low-, or high-density lipoprotein cholesterol.³ An important observation was made by Stein et al.²⁶ who found that verapamil, in concentrations of 10 to 50 $\mu\text{mol/L}$ increased the receptor-mediated endocytosis of LDL by aortic smooth muscle cells in culture, thereby promoting degradation of LDL. Another possible cellular mechanism that may be related to the antiatherogenic potential of calcium antagonists in animal models has been shown by Etingin and Hajjar.²⁷ They demonstrated that physiologic concentrations (10 to 100 $\mu\text{mol/L}$) of nifedipine doubled the activity of rabbit smooth muscle cell lysosomal hydrolysis of cholesterol esters.

The pharmacologic effects of calcium antagonists include negative inotropic and vasodilating actions. Therefore the reported antiatherogenic effects of these compounds may be related to a hemodynamic factor through lowering of blood pressure. However the results of this study demonstrated a significant reduction in the amount of intimal hyperplasia in vein grafts without any effect on the blood pressure of the experimental animals. This is in accordance with a study by Blumlein et al.,²⁸ which concluded that the antiatherogenic properties of verapamil are not a result of lowering blood pressure. Further support comes from the work of Handley⁹ who has documented the ability of the experimental calcium antagonists PN200-110 and PY108-068 to produce similar reductions in neointimal lesion development in the balloon-injured rat carotid artery, despite disparate effects of these compounds on blood pressure. Therefore it is unlikely that reduction in blood pressure is responsible for the inhibition of intimal hyperplasia by calcium antagonists.

The importance of platelet-vessel wall interactions after endothelial denudation is well recognized. Platelets are also considered to be an important mediator of detrimental events in vein graft failure, *i.e.*, thrombogenesis and progressive intimal hyperplasia.²⁹ Srivastava³⁰ has reported the ability of nifedipine, verapamil, and hydralazine to inhibit aggregation of human platelets in the presence of ADP, epinephrine, collagen, or arachidonate. Therefore one might speculate that calcium antagonists may reduce intimal hyperplasia by inhibiting platelet aggregation stimulated by collagen exposed in the subendothelium after endothelial injury. Such a mechanism would reduce the amount of PDGF entering the artery wall. However the reported antiplatelet effects of verapamil are seen with doses on the order of 20 $\mu\text{mol/L}$,^{31,32} and in our studies the mean plasma verapamil levels were 50.9 ng/mL, which is equivalent to 0.103 $\mu\text{mol/L}$. This verapamil level is several times less than the effective an-

tiplatelet level, so it is unlikely that the plasma verapamil concentration in our study inhibited intimal hyperplasia by antiplatelet action. This is further supported by our results of *in vitro* platelet aggregation to ADP, which showed no difference between the control and experimental groups. Further support for the lack of an antiaggregatory effect of calcium antagonists in the decreased development of intimal hyperplasia comes from two recent studies. These studies showed that although platelet adherence begins within minutes and persists for hours,²⁹ nifedipine in a single dose given 20 hours after balloon catheter injury was still effective in reducing intimal hyperplasia.⁷ In addition, in our study the steady state level of verapamil would not be expected to occur until 24 hours after grafting because the infusion of verapamil was started at the time of surgery.

Furthermore in this study we have demonstrated that experimental vein grafts treated with verapamil for 28 days become more sensitive to norepinephrine and histamine as compared to control vein grafts, but the reactivity to serotonin was unaltered. Similarly verapamil treatment induced supersensitivity to norepinephrine and histamine in normal veins as compared to the saline-treated normal veins. As an explanation for the altered vasoreactivity that has been shown in this study in verapamil-treated vessels, we tested whether verapamil treatment affected EDRF production in these vessels. Although vein grafts from both groups could not relax in response to acetylcholine, there was no difference in the endothelium-mediated relaxation in normal veins from both groups, indicating that modulation of EDRF production by verapamil is unlikely.

The increased sensitivity of treated vein grafts and normal veins to norepinephrine and histamine may be related to upregulation of the calcium channels in these vessels or to a quantitative or qualitative change in the receptors for these agonists induced by chronic verapamil therapy. Several recent reports have indicated that different calcium antagonists may exert a blocking effect on membrane receptors.^{33,34} Karliner³⁵ has found that verapamil is a competitive antagonist of α_1 -adrenergic and muscarinic receptors but not of beta-adrenergic receptors. The precise relationship between the actions of verapamil at the calcium channels and its effects on specific membrane receptors is not clear. It is interesting to note that the effects of both α_1 -adrenergic and muscarinic agonists in a variety of tissues appear to be mediated through increases in calcium influx,³⁶ suggesting an association between these receptors and membrane calcium channels. Thus the antagonistic effects of verapamil on physiologic responses to pharmacologic agents may be due both to inhibition of the slow calcium channel and to direct receptor effects.

An intriguing finding in this study was the contractile

response of normal veins treated with verapamil in response to serotonin, while none of the normal veins in the control group responded. The possibility of an involvement of α_1 -receptors in the response of verapamil-treated normal vein to serotonin is unlikely because phentolamine did not alter the response (data not shown). Further studies are needed to clarify the effects of verapamil therapy on vasomotor function.

Because we could not demonstrate any difference in platelet or endothelial function between untreated and verapamil-treated animals, we examined the direct effect of verapamil on smooth muscle. Verapamil significantly inhibited [^{3} H]-thymidine incorporation into DNA in vascular smooth muscle cells in culture.

Smooth muscle cell proliferation, migration, and synthesis of connective tissue proteins, under the influence of different mitogenic factors, are now considered the major processes in the formation of intimal hyperplasia.¹⁶ Therefore interference with these events might have a beneficial role in reducing the amount of intimal hyperplasia after endothelial injury. In the proliferative intimal hyperplastic response, the synthetic phenotype of smooth muscle cells plays a major role. Recently phenotypic modulation of smooth muscle cells from the contractile, nonproliferative phenotype to the synthetic, proliferative phenotype of cells shown to be inhibited by calcium antagonists.³⁷ Furthermore it has been demonstrated that the proliferative response of smooth muscle cells in response to growth factors, including the PDGF, has been altered by calcium antagonists. In addition *in vitro* studies have shown inhibition of smooth muscle cell migration using calcium antagonists.¹⁸

Our experiments with verapamil confirmed a significant dose-dependent inhibition of DNA synthesis in vascular smooth muscle cells in culture. The dose of verapamil needed to show significant inhibition in DNA synthesis was 50 times that of the *in vivo* verapamil concentration. This may be related, in part, to the fact that the smooth muscle cells were maximally stimulated in the *in vitro* experiment, and that this was a single acute administration of verapamil *in vitro*, as opposed to chronic treatment *in vivo*. Therefore the beneficial effects of verapamil therapy on the development of intimal hyperplasia may be related to inhibition of smooth muscle cell reactions. Further support for this hypothesis comes from the recent results of an *in vivo* study that showed that incorporation of [^{3} H]-thymidine into DNA of rat aortic smooth muscle cells 48 hours after balloon injury was significantly reduced by therapeutic doses of nifedipine, verapamil, diltiazem, or lanthanum.¹⁹

Recently Cole et al.³⁸ demonstrated that polymorphonuclear leukocytes produce a factor that causes smooth muscle cells to increase [^{3} H]-thymidine incorporation into DNA *in vitro*, and demonstrated that *in vitro*³⁹ PMNs and

their products are significantly associated with areas of endothelial denudation. It is interesting that verapamil has been shown to inhibit chemotaxis, phagocytosis, aggregation, degranulation, and superoxide production in neutrophils,⁴⁰ and therefore also may reduce the proliferative stimulus for the smooth muscle cells.

This study shows that 28-day verapamil therapy has a significant effect in reducing the amount of intimal hyperplasia in experimental vein bypass grafts. This may be due to direct inhibition of smooth muscle cell proliferation. The involvement of total serum cholesterol concentration, blood pressure, or platelet aggregation in reducing intimal hyperplasia by verapamil seems unlikely. An interesting finding was the development of enhanced reactivity of both vein grafts and normal veins after verapamil treatment, even though vein grafts are less sensitive than normal veins. The ability of verapamil-treated normal veins to produce EDRF is unaltered. However, despite the enhanced reactivity that developed after verapamil treatment, the patency rate was the same in both groups. Therefore the dose of verapamil used to produce a significant inhibition of intimal hyperplasia may contribute to improved long-term patency in vein bypass grafts.

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Selective Shunt *Versus* Nonshunt Surgery for Management of Both Schistosomal and Nonschistosomal Variceal Bleeders

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This clinical study included 219 (Child A/B) consecutive variceal bleeders. Electively 123 had distal splenorenal shunt (DSRS) and 96 had splenectomy with gastroesophageal devascularization (S&GD). Liver pathology was documented in 73% of patients, with schistosomal fibrosis in 41% and nonalcoholic cirrhosis or mixed pattern (fibrosis and cirrhosis) in 59%. The surgical groups were similar before operation, with a mean follow-up of 82 ± 13 and 78 ± 18 months, respectively (range, 60 to 120 months). The two pathologic populations were also similar before each and both procedures. The operative mortality rates were low, with incidences of 3.3% (DSRS) and 3.1% (S&GD). Rebleeding occurred significantly ($p < 0.05$) more frequently after S&GD (27%) compared to DSRS (5.7%). Sclerotherapy salvaged 65% of S&GD rebleeders. Encephalopathy developed significantly ($p < 0.05$) more after DSRS (18.7%) compared to S&GD (7.3%), with no significant difference among the current survivors. The difference in overall rebleeding and encephalopathy rates between both procedures was statistically related to patients with cirrhosis and mixed lesions ($p < 0.05$). Distal splenorenal shunt significantly reduced the endoscopic variceal size more than S&GD ($p < 0.05$). Prograde portal perfusion was documented in 94% of patients in each group, with a variable distinct pattern of portovenal collaterals in 91% (DSRS) and 65% (S&GD). The total population cumulative survival was similar with 80% for DSRS and 79% for S&GD (plus sclerosis in 23%), with hepatic cell failure the cause of death in 46% and 50%, respectively. However, in the schistosomal patients, survival was better improved after DSRS (90%) compared to S&GD (75%), with no difference among the cirrhotic and mixed group (DSRS 73%, S&GD 72%). In conclusion (1) both DSRS and S&GD have low operative mortality rates, (2) DSRS is superior to S&GD in the schistosomal patients, and (3) S&GD backed by endosclerosis for rebleeding is a good surgical alternative to selective shunt in the nonalcoholic cirrhotic and mixed population.

GREAT CONTROVERSY STILL exists over the current therapeutic strategies for variceal bleeding, especially when surgery is considered.^{1,2} The resurgence of old and the introduction of new modalities

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have exacerbated the dispute.³ Despite the encouraging current results and efficacy of sclerotherapy, surgery still has a definitive place for challenging management of these patients.⁴⁻¹³

The introduction of selective shunts in the late 1960s extended the range of surgical options beyond the previously known surgical modalities, total shunts and portosystemic disconnection procedures.^{14,15} Despite the effective control of variceal hemorrhage, total shunts were associated with a prohibitive incidence of devastating encephalopathy and hepatic failure that threatened patient survival, especially in the nonalcoholic cirrhotics and schistosomal population.¹⁶⁻²² Therefore the alternative approach of splenectomy with different gastroesophageal devascularization techniques has emerged.²³⁻³⁰ The high risk of variceal rebleeding after such nonshunt procedures, especially among the western populations, further triggered the introduction of both distal splenorenal and coronocaval shunts.^{23,26,28,31,32}

With the potential advantages of preserving portal perfusion and hepatocyte functions, distal splenorenal shunt (DSRS) offers an alternative procedure to splenectomy with gastroesophageal devascularization (S&GD), which is still the most popular type of portal hypertensive surgery in Egypt.^{33,34} The worldwide experience with DSRS has been carefully analyzed, compiled, and reported in the literature.³⁴⁻⁴² However only few scattered publications have comparatively addressed the results of both surgical modalities because of the western dissatisfaction with nonshunt surgery.^{43,44}

The main objective of this current study, therefore, is to competitively evaluate the long-term therapeutic effects of these two surgical procedures in response to the underlying chronic liver disease.

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Materials and Methods

Patient Population

The study population comprised 219 variceal bleeders managed by elective surgery in the period between April 1979 and April 1984 at the Gastroenterology Unit of Mansoura University Hospital, Egypt. Consecutively 123 patients received selective DSRS and 96 S&GD. The patients subjected to this study represented 65% of a larger total population of 335 seen during the same period of time and managed electively with other surgical therapeutic modalities: splenectomy and left gastric vasoligation (25%), stapler esophageal transection (8%), and total as well as coronorenal shunts (2%). All patients included in the study fulfilled the following criteria: (1) history of at least one major episode of variceal hemorrhage with a 4- to 6-week interval between the last attack and date of surgery, and (2) no symptoms or signs suggestive of encephalopathy. Bilharzial corpulmonale, concomitant chronic duodenal ulcers, and unsuitable venous anatomy were criteria of DSRS exclusion. The characteristics of the two surgical groups are summarized in Table 1. They were matched for all of the preoperative data base except for total bilirubin.

Surgical Techniques

The standard selective shunt (DSRS) was applied as described by Warren et al.,¹⁴ with interruption of the pathways connecting the gastrosplenic compartment to the portomesenteric axis. The technique of gastroesophageal decongestion with splenectomy as described by Hassab²⁴ was adopted with more extensive devascularization along the right gastroepiploic arcade. Complete

interruption of the coronary system and devascularization of the lower 5 to 7 cm of the esophagus without transection were essential parts of the technique. Surgical drainage of the stomach was routine in the first 22 patients, with pyloroplasty in 18 and gastrojejunostomy in 4. For definitive treatment of concomitant chronic duodenal ulcer, proximal gastric vagotomy was completed in 17 and truncal vagotomy with gastrojejunostomy was added in four patients.

Preoperative and Postoperative Evaluations

All subjected patients were carefully studied before surgery. In addition to the longitudinal follow-up every year, comprehensive evaluations were completed in the last follow-up, with a minimum of 5 years for all survivors.

Clinical and Biochemical Examinations

Thorough history and physical examination were done, with special attention to episodes of recurrent hemorrhage, jaundice, ascites, encephalopathy, and employment or activity status. Routine laboratory tests included hemogram, serum albumin, total bilirubin, prothrombin time, AST (SGOT), ALT (SGPT), blood urea nitrogen, creatinine, and serum electrolytes. The previous parameters were the basis for stratifying the patients into Child's classes before surgery.

Endoscopy

Upper fiberoptic endoscopic examination was done to identify and grade the esophagogastric varices and to detect any associated upper gastrointestinal lesions. Variceal

TABLE 1. Preoperative Clinical and Biochemical Definitions of the Surgical Groups and Pathologic Subsets

Definition	Total Population		Schistosomal Hepatic Fibrosis		Cirrhosis ± SHF*	
	DSRS	S & GD	DSRS	S & GD	DSRS	S & GD
No. of patients	123	96	50	16	44	50
Age (years)	36 ± 11	36 ± 11	31 ± 9	30 ± 10	38 ± 12	40 ± 11
Sex						
Male	120	87	50	15	42	46
Female	3	9	—	1	2	4
Variceal grade						
I	8%	8%	5%	7%	9%	8%
II	29%	27%	30%	25%	27%	28%
III	63%	65%	65%	68%	64%	64%
Child's A/B	112/11	78/9	49/1	48/2	40/4	44/6
Follow-up (months)	82 ± 13	78 ± 18	81 ± 15	73 ± 22	79 ± 12	73 ± 14†
Albumin (3–5.2 g/dL)	4.0 ± 0.6	4.0 ± 0.5	4.0 ± 0.6	4.0 ± 0.5	4.0 ± 0.6	4.0 ± 0.5
Total bilirubin (0.2–1.2 mg/dL)	1.0 ± 0.4	1.2 ± 0.6†	1.0 ± 0.6	1.3 ± 0.7	1.0 ± 0.4	1.3 ± 0.6†
Protime (+ sec)	1.6 ± 1.4	1.9 ± 1.5	1.5 ± 1.1	1.9 ± 1.3	1.6 ± 1.6	2.1 ± 1.7
AST (3–25 IU/L)	46 ± 27	49 ± 29	46 ± 22	55 ± 47	54 ± 35	52 ± 25
ALT (5–26 IU/L)	37 ± 32	42 ± 31	42 ± 40	54 ± 54	41 ± 27	43 ± 21
Alk. phosph. (5–13 KAU/L)	10 ± 6	10 ± 6	11 ± 8	11 ± 6	11 ± 5	11 ± 7

Normal values in parenthesis; SHF, schistosomal hepatic fibrosis.

* Activity: DSRS, 57%; S & GD 62%.

† $p < 0.05$.

grading was done before and after surgery by the same team adopting one system.⁴⁵ In addition to the endoscopic surveillance of all patients every year, emergent or sometimes urgent examinations were done for most of the postoperative variceal rebleeders.

Hemodynamic and Radiologic Studies

Intravenous urography and abdominal ultrasonography were done for most patients for preoperative assessment of the renal and hepatobiliary systems, liver size, and architecture. Percutaneous transplenic portography was done in 90 of the DSRS patients 3 to 6 months after surgery. Also 51 patients had visceral angiography (DSRS, 34; S&GD, 17) at the time of last follow-up. The angiographic package included the standard superior mesenteric (SM) study in both surgical groups and the splenic artery or shunt catheterization for visualization of the shunt. The portal perfusion grade was assessed from the venous phase of the SM angiogram (grade I, prograde flow to grade IV, absent portal flow).⁴⁶

Cardiopulmonary Assessment

Cardiopulmonary assessment was essential before and after surgery for detection of bilharzial cor pulmonale and pulmonary hypertension. Evaluation included thorough clinical examination with electro- and echocardiography in selected cases.

Neuropsychiatric Evaluation

Clinical examination and electroencephalogram (EEG) were done before and every year after surgery by the neuropsychiatric department. Abnormal EEG was diagnosed and graded by the criteria of Parsons-Smith.⁴⁷ Venous blood ammonia was measured in the fasting state.

Hepatic Pathology

Preoperative Tru-Cut needle and/or operative wedge biopsy were done in 160 (73%) variceal bleeders. The histopathologic criteria of schistosomal hepatic fibrosis (SHF) were evident in 66 (41%) patients (DSRS, 50; S&GD, 16). The other 94 (59%) showed nonalcoholic cirrhosis $\pm$ SHF (DSRS, 44; S&GD, 50) with morphologic evidence of chronic activity in 57% (DSRS) and 62% (S&GD). The similar surgical outcome in each of the cirrhotic and mixed cohorts in our previously published study⁴⁸ was the bases of adding both pathologic entities into one subset. The preoperative data for the two main pathologic subsets did not show any significant difference in and between both surgical groups, except for the total bilirubin among the cirrhotic and mixed cohort (Table 1).

Sclerotherapy

Endoscopic variceal sclerosis was emergently conducted in 22 variceal rebleeders after S&GD, representing 23% of the total patients, with chronic therapy in 19. It was done by a flexible endoscope using ethanolamine oleate (5%) as sclerosant for combined intra- and paravariceal injections.

Definitions

Hospital (operative) mortality was defined as death within 30 days of surgery or death occurring in the same hospitalization as surgery.

Rebleeding was defined as at least a two-unit blood transfusion requirement and/or a decrease in the hematocrit to less than 30%.

Clinical encephalopathy was defined as an episode of mental confusion clearly related by the patient or a family member or detection of disorientation by a neurologist. Disorientation or coma appearing just before death from hepatic failure was excluded. The degree was clinically graded as mild, moderate, and severe.⁴⁸

Therapy Failure

Hepatic disease and surgical related mortalities were considered failure of therapy for both procedures. Also change or addition of therapy among survivors due to shunt dysfunction and/or variceal rebleeding was included.

Statistical Analysis

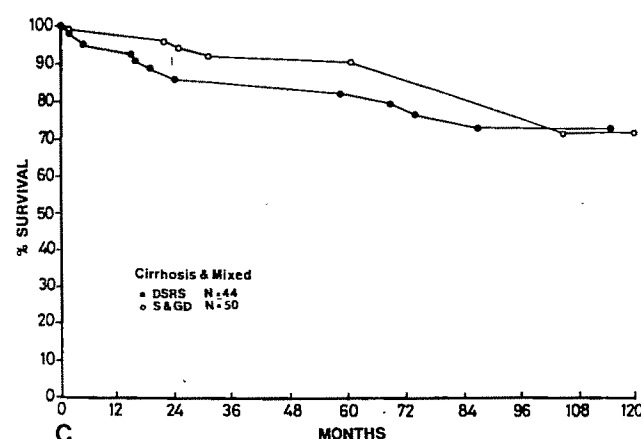
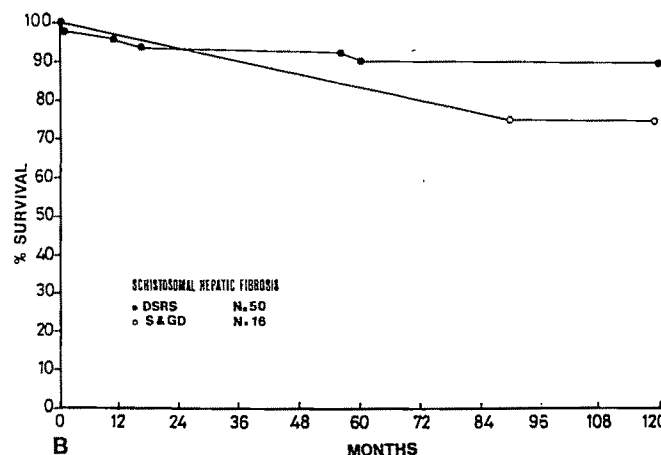
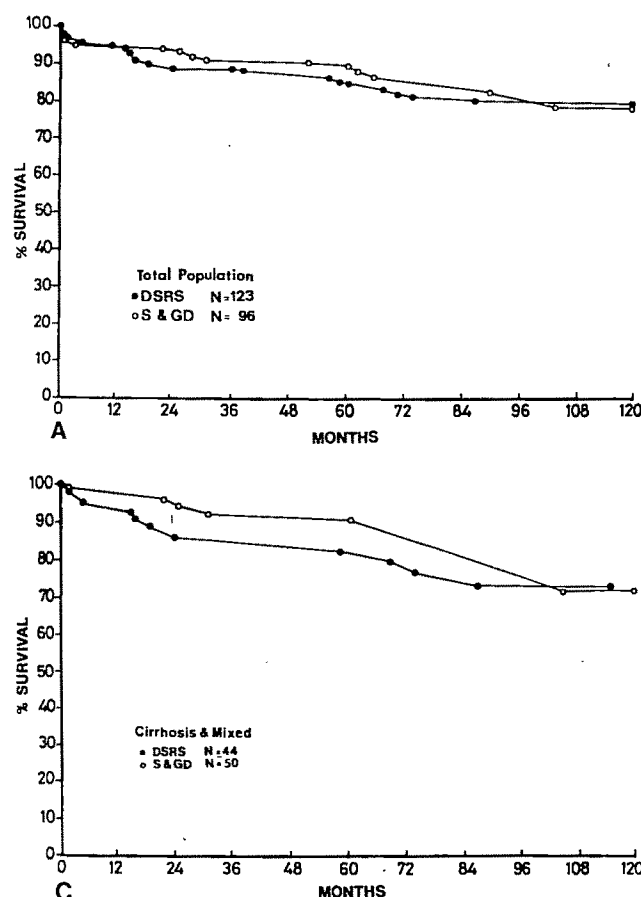
Data was computed for the total population and pathologic cohorts in each surgical group. The Kaplan-Meier method was used to plot survival and failure of therapy curves,^{49,50} which were compared, among the surgical and pathologic groups, by the log-rank test.⁵⁰ Groups were compared before operation by the unpaired t test (quantitative data) and chi-square analysis (qualitative data). Serial variables within each group were analyzed by the paired t test.⁵¹

Results

Survival

Hospital death occurred in four (3.3%) of the DSRS and three (3.1%) of the S&GD patients. Hemostatic failure ($n = 2$) and septicemia ($n = 2$) in the first group with hepatic failure ($n = 2$) and pulmonary embolism ($n = 1$) in the second group were the causes of operative death.

The survival curves for the two surgical groups (Fig. 1A) showed similar cumulative rates (DSRS, 80%; S&GD, 79%), with a mean follow-up of 82 ± 13 and 78 ± 18 months, respectively. However it must be mentioned that



FIGS. 1A-C. Kaplan-Meier survival plot for DSRS and S&GD patients. (A) The curves for total population are not different at any time interval, with a cumulative rate of 80% (DSRS) and 79% (S&GD + 23% sclerotherapy). (B) The schistosomal patients have better 9-year survival rate after DSRS (90%) compared to S&GD (75%; $p > 0.05$). (C) The cirrhotic and mixed group has a similar cumulative survival rate after both DSRS (73%) and S&GD (72%).

sclerotherapy was required for 23% of S&GD patients for the management of variceal rebleeding. Splitting of these cumulative curves that describe survival according to the underlying hepatic pathology declared better survival of the schistosomal patients after DSRS (90%) compared to S&GD (75%), with $p > 0.05$ (Fig. 1B). The cirrhotic and mixed group had no difference between therapies for this index, with rates of 73% and 72%, respectively (Fig. 1C).

The common cause of death was hepatic cell failure after both procedures, with an incidence of 46% (DSRS) and 50% (S&GD). Chronic active liver disease was histologically documented in 38% and 25% of these deaths, respectively. The other different causes of total deaths are listed in Table 2.

Failure of Therapy

Failure of therapy curves for the two surgical groups are shown in Figure 2A. The difference achieved a significant value at 72 months, with more failure after S&GD ($p < 0.05$). Shunt failure developed in 11 patients, mostly in the early postoperative period, with detection of shunt thrombosis in a total of nine patients (7.3%), and only six of them developed variceal rebleeding. The remaining two patients rebled, which proved to be variceal, with earlier

documentation of shunt patency in one, giving a total recurrent variceal hemorrhage rate of 5.7%. The anastomosis was salvaged by early refashioning in one patient and splenectomy plus devascularization was successfully performed in five. The other five were included in the total deaths with exsanguination ($n = 2$), trial of mesocaval shunt ($n = 1$), septicemia ($n = 1$), and automobile injury ($n = 1$) as the causes of death.

TABLE 2. Causes of Death

Cause	DSRS		S & GD	
	No.	%	No.	%
Hemostatic failure	2	7	0	0
Pulmonary embolism	0	0	1	6
Hepatic cell failure	13	46	8	50*
Variceal hemorrhage	2	7	3	19*
Septicemia	3	11	0	0
Hepatocellular carcinoma	2	7	2	13
Mesenteric vascular occlusion	0	0	1	6
Trial of mesocaval shunt	1	4	0	0
Complication of transplenic portography	1	4	0	0
Irrelevant	2	7	0	0
Undetermined	2	7	1	6

* $p > 0.05$.

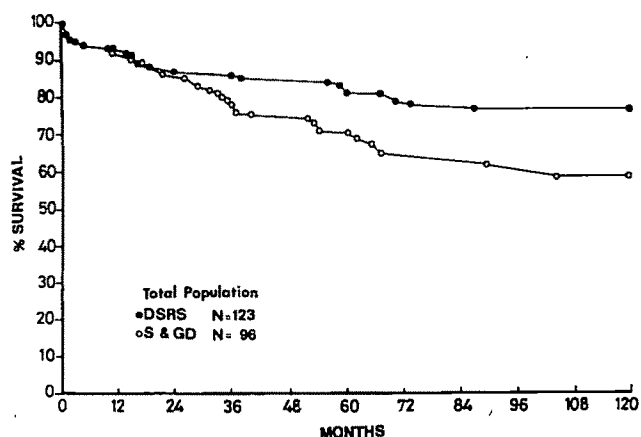


FIG. 2. Kaplan-Meier plot of therapy failure after DSRS and S&GD. A significant difference ($p < 0.05$) was detected only at and after 72 months.

Variceal hemorrhage was the cause of therapy failure after S&GD in 26 patients. Emergent sclerotherapy was conducted in 22 cases and was successful in 19 (86%) and balloon tamponade was life saving in 2. Exsanguination was unavoidable in three patients and recurrent bleeding episodes precipitated hepatic cell failure in six. Chronic sclerotherapy salvaged the other 17 patients, with a rate of 65%. They received 4.2 ± 1.9 sclerosing sessions and the varices were completely obliterated in 35% of these patients.

Recurrent Hemorrhage

Recurrent upper gastrointestinal bleeding developed, with a total incidence of 7.3% after DSRS ($n = 9$) and 31% after S&GD ($n = 30$). In the selective shunt group, in addition to those who have been discussed with therapy failure, only one patient with patent shunt developed fundic bleeding 8 days after surgery and was managed conservatively.

The source of bleeding after S&GD was endoscopically documented in 29 patients: 26, variceal; erosive gastritis, 2; and chronic duodenal ulcer, 1. Variceal hemorrhage (27%) was mild to moderate in 21 and life threatening in only five cases. The endoscopic stigmata of variceal bleeding were actual venous spurts (27%), venous oozes (38%), and adherent clots (35%). The onset of rebleeding ranged from 1 to 85 months, with a mean of 32 ± 22

months. Erosive gastric bleeding was frequent but mild in severity. The two patients were managed conservatively and hepatic cell failure was precipitated in one. The patient with chronic active duodenal ulcer required truncal vagotomy and gastrojejunostomy and that with undocumented source was successfully managed by simple conservative measures.

The incidence of variceal rebleeding was different among the two pathologic groups. It was 10% for the schistosomal and 2% for the cirrhotic and mixed groups after DSRS ($p = 0.01$). With S&GD the cirrhotic and mixed cohort had more but nonsignificant rebleeding rate (38%) compared to the schistosomal patients (19%; $p = 0.2$). Comparing both procedures, the difference was statistically significant among the cirrhotic and mixed but not in the schistosomal patients ($p < 0.05$). Within each surgical group, there was no single preoperative variable, including the variceal grades that significantly predict the recurrence of variceal bleeding.

Encephalopathy

None of the studied patients experienced clinical encephalopathy before surgery. The total incidence of postoperative encephalopathy was significantly higher ($p = 0.02$) after DSRS (18.7%) compared to S&GD (7.3%), with no significant difference among current survivors. The descriptive clinical, pathologic, and neuropsychiatric data are listed in Table 3. The onset was earlier and the degree was more severe after DSRS.

The attack rate of encephalopathy after DSRS varied when applied to the underlying liver disease. The difference was statistically significant ($p = 0.03$), with an incidence of 10% for the schistosomal and 27% for the cirrhotic and mixed populations. With S&GD both pathologic entities have the same morbidity rate of 6%. Comparing both procedures, the cirrhotic and mixed, but not the schistosomal, population showed a significantly higher incidence after DSRS ($p = 0.005$).

Biochemical Data

The conventional measures of hepatocyte functions were analyzed before surgery and at the time of last follow-up for all survivors in each group (Table 4). There was a significant increase in ALT (SGPT) and alkaline phos-

TABLE 3. Clinical Encephalopathy After DSRS and S & GD

Surgical Modality	No. of Patients			Onset Range (mos.) (mean $\pm$ SD)	Clinical Degree			Fasting Ammonia μ g/dL	Abnormal EEG	Survivors
	Total	SHF	C $\pm$ SHF		Mild	Mod.	Severe			
DSRS	23 (18.7%)	5 (10%)	12 (27%)	3-67 (23 $\pm$ 16)	4 (17%)	8 (35%)	11 (48%)	204 $\pm$ 91 (n = 19)	83% (n = 22)	10 (43%)
S & GD	7 (7.3%)	1 (6%)	3 (6%)	12-80 (32 $\pm$ 23)	4 (57%)	2 (29%)	1 (14%)	198 $\pm$ 112 (n = 4)	71% (n = 5)	4 (57%)

SHF, schistosomal hepatic fibrosis; C, cirrhosis.

TABLE 4. Five- to Ten-year Postoperative Biochemical Changes Among Total Survivors in Both Surgical Groups

	DSRS (n = 87)		S & GD (n = 79)	
	Before	After	Before	After
Albumin (3–5.2 g/dL)	4.1 ± 0.5	4.0 ± 0.6	4.0 ± 0.5	4.0 ± 0.6
Bilirubin (0.2–1.2 mg/dL)	1.0 ± 0.4	1.7 ± 0.9*	1.2 ± 0.6	1.1 ± 1.2
Protime (+ sec)	1.6 ± 1.5	1.5 ± 1.3	1.9 ± 1.4	0.9 ± 1.2*
AST (3–25 IU/L)	45 ± 26	47 ± 25	49 ± 29	53 ± 38
ALT (5–26 IU/L)	38 ± 33	48 ± 31*	42 ± 32	55 ± 45*
Alk. phosph. (5–13 KAU/L)	10 ± 6	12 ± 5*	11 ± 7	13 ± 5*

* p value < 0.05.

phatase in both surgical groups, with significant increase in total bilirubin after DSRS and reduction in prothrombin time (+ sec) after S&GD ($p < 0.05$). There were no significant changes in the other biochemical parameters.

The biochemical profile for the schistosomal survivors showed significant changes in total bilirubin, with increase after DSRS and reduction after S&GD ($p < 0.05$). In addition prothrombin time (+ sec) was significantly reduced after S&GD ($p < 0.05$). The serum enzymes did not show any significant changes with each surgical procedure (Table 5). Meanwhile the cirrhotic and mixed survivors showed significant ($p < 0.05$) increase in total bilirubin after DSRS and ALT as well as alkaline phosphatase after S&GD (Table 6). Prothrombin time (+ sec) was significantly reduced after S&GD ($p < 0.05$). Interestingly the changes in serum enzymes after S&GD among the total population were statistically linked to the cirrhotic and mixed cohort.

Ascites

Early postoperative ascites developed in 28 (23%) patients after DSRS and in 12 (13%) patients after S&GD. Salt restriction and diuretic therapy controlled ascites in most of these surgical patients within the first year. At the time of last follow-up, ascites was detected in seven (7.4%) DSRS and four (5%) S&GD survivors.

Reduction of Variceal Sizes

Both DSRS and S&GD reduced the endoscopic size of esophageal varices among survivors. The collective quan-

titative reduction and that of each preoperative grade was more significant ($p < 0.05$) after DSRS. The endoscopic disappearance of varices showed a significant ($p = 0.003$) difference comparing DSRS (37%) to S&GD (18%).

Hemodynamic Data

Prograde portal perfusion was documented in 94% of the angiographically studied patients at 5 to 10 years after each surgical procedure (Figs. 3A and B). Impaired or lost portal perfusion after both techniques mainly was due to splenorenal stealing in the DSRS and portal vein thrombosis in the S&GD group. Angiographically portal vein thrombosis was detected in three (18%) S&GD patients, with development of cavernous malformation in two. Portal perfusion grading was I to II in 82% of both DSRS and S&GD patients, with more cases of grade I after selective shunt (Fig. 4).

Portapival collaterals were detected in 91% (DSRS) and 65% (S&GD) of the studied patients. The pattern was different among both groups. The pancreatic collaterals were documented only after DSRS, with an incidence of 50%. The portogastric pathways were common after both procedures, with more incidence (65%) after S&GD.

Discussion

No single therapy has been rationally recognized as an ideal approach for all portal hypertensive variceal bleeders. The choice of therapy for these patients, then, must be based on the balance of risks between recurrent bleeding, encephalopathy, and hepatic failure.³⁵ Identification of

TABLE 5. Changes in the Biochemical Data of the Schistosomal Survivors

	DSRS (n = 38)		S & GD (n = 15)	
	Before	After	Before	After
Albumin (3–5.2 g/dL)	4.1 ± 0.6	4.1 ± 0.6	4.0 ± 0.5	4.1 ± 0.4
Bilirubin (0.2–1.2 mg/dL)	1.0 ± 0.5	1.9 ± 1.2*	1.4 ± 0.7	1.0 ± 0.4*
Protime (+ sec)	1.5 ± 1.2	1.4 ± 1.3	2.0 ± 1.0	0.9 ± 1.0*
AST (3–25 IU/L)	46 ± 24	43 ± 25	53 ± 47	34 ± 13
ALT (5–26 IU/L)	41 ± 41	41 ± 29	53 ± 55	51 ± 54
Alk. phosph. (5–13 KAU/L)	11 ± 8	12 ± 6	11 ± 6	11 ± 5

* p value < 0.05.

TABLE 6. Changes in the Biochemical Profile of Hepatic Function for the Cirrhotic and Mixed Survivors

	DSRS (n = 30)		S & GD (n = 43)	
	Before	After	Before	After
Albumin (3–5.2 g/dL)	4.2 ± 0.4	4.0 ± 0.7	4.0 ± 0.5	4.0 ± 0.7
Bilirubin (0.2–1.2 mg/dL)	1.1 ± 0.4	1.5 ± 0.6*	1.3 ± 0.6	1.2 ± 1.6
Protine (+ sec)	1.7 ± 1.8	1.4 ± 1.3	2.1 ± 1.5	0.9 ± 1.3*
AST (3–25 IU/L)	52 ± 30	54 ± 26	50 ± 23	57 ± 42
ALT (5–26 IU/L)	44 ± 27	56 ± 37	42 ± 20	54 ± 42*
Alk. phosph. (5–13 KAU/L)	11 ± 5	12 ± 5	12 ± 8	14 ± 6*

* p value < 0.05.

the optimal modality for each population may significantly enhance the therapeutic outcome and overall survival. This current unicentric study exemplifies and proves such therapeutic wisdom by addressing the long-term clinical, biochemical, and hemodynamic effects of both selective shunt and splenectomy with gastroesophageal devascularization in patients with different forms of portal hypertension.

Both distal splenorenal shunt (DSRS) and splenectomy with gastroesophageal devascularization (S&GD) have the same aim to prevent variceal hemorrhage, maintain portal perfusion, and preserve hepatocyte functions.^{14,24} These objectives may be best evaluated in the schistosomal population. The uniformity of the hepatic fibrosis process in these patients may minimize the large number of variables inherent in cirrhotic patients.⁴⁸

The therapeutic goals of both procedures are mainly achieved by selective reduction of the intravariceal pressure. The mechanism of creating this segmental hemodynamic pattern is different with each procedure. Splenectomy with gastroesophageal devascularization directly interrupts the extramural gastroesophageal collateral blood flow to the varices, while DSRS creates a low-pressure drainage pathway by diverting the short gastric venous flow to the renal vein *via* the splenic venous system. Therefore DSRS seems to decompress while S&GD decongests the variceal channels.

Some technical and physiologic aspects of both procedures must be addressed and clarified. First the large size of the spleen does not preclude the performance of DSRS.^{34,40} Second, with the operative detection of massive splenic vascular adhesions, proceeding with S&GD may carry higher rates of surgical mortality and morbidity. Finally the reported long-term risks of splenectomy may outweigh the better response of hypersplenism to non-shunt surgery.^{52–57}

Elective DSRS and S&GD were associated with similar and acceptable operative risks in preoperative Child A/B patients. This further supports most of the worldwide published experiences with both procedures.^{35,58,59} Pancreatitis after DSRS and subphrenic collections af-

ter S&GD are technique-related specific morbidities that sometimes complicate the early postoperative course.^{52,60,61}

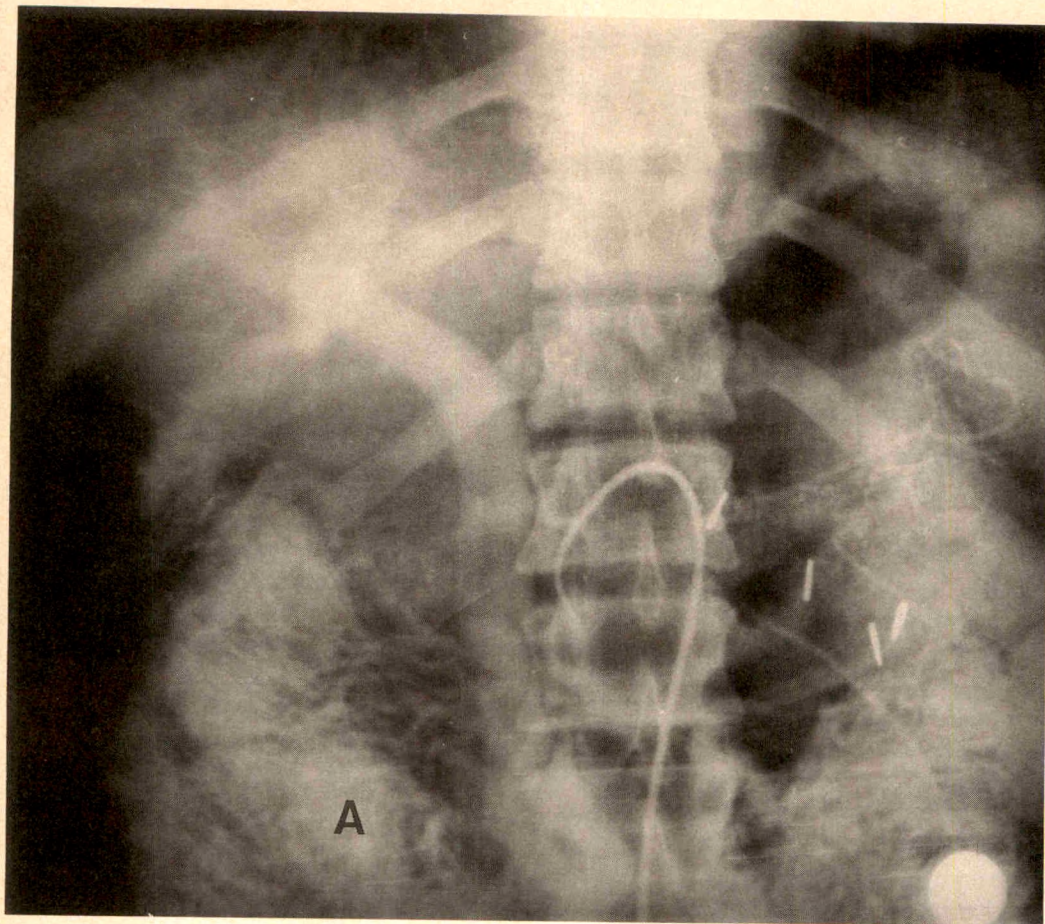
Successful management of variceal bleeders is primarily threatened by the recurrence of hemorrhage. The significant difference in therapy failure with both procedures was mainly attributed to the higher incidence (27%) of rebleeding after S&GD. This difference, together with more significant reduction of the endoscopic variceal sizes, indicate the superiority of DSRS in decompressing the gastroesophageal varices. The persistent high pressure in the portal system, including the gastroesophageal collaterals after S&GD, triggers the relentless formation of new varices with increased incidence of rebleeding.²³

Existence of the portal hypertensive gastropathy manifested by frequent minor episodes of upper gastrointestinal hemorrhage was evident in two patients after S&GD. This may be related to the documented gastric vascular changes associated with the high portal venous pressure in cirrhotic patients.^{62–65}

Sclerotherapy effectively controlled the hemorrhage in 86% of the emergently sclerosed patients and salvaged 65% of variceal rebleeders after S&GD. The low risk of catastrophic uncontrollable hemorrhage in these patients can be attributed to the decongestive effect of the devascularization procedure with interruption of the coronary system and paraesophageal perforators.^{66–69}

Recurrent hemorrhage in DSRS patients was commonly associated with shunt occlusion and early correction with refashioning or gastroesophageal devascularization is strongly recommended. With S&GD none of the preoperative parameters, including the endoscopic variceal grades, were statistically reliable discriminators for rebleeding.

Maintenance of portal perfusion is essential for preservation of the metabolic integrity of hepatocytes. Although DSRS has received extensive angiographic and quantitative hemodynamic studies, none of the available literature has addressed such data after S&GD.^{36,70–79} In this series the late angiographic studies demonstrated prograde portal flow in 94% of both DSRS and S&GD pa-



FIGS. 3A and B. Venous phase of superior mesenteric angiogram. Grade I portal perfusion with no collaterals (A) 9.5 years after DSRS and (B) 9 years after S&GD.

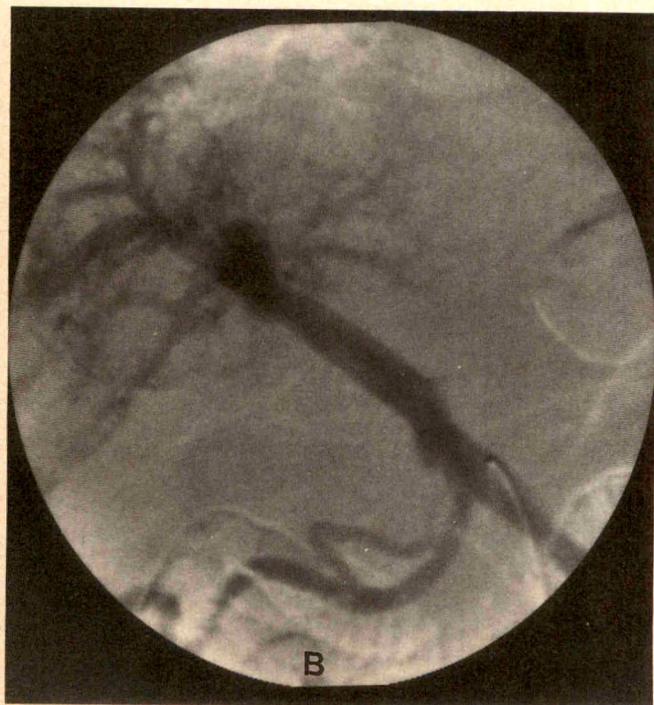


FIG. 3. (Continued)

tients. Loss of hepatopetal flow was mainly due to development of portal malcirculation after DSRS and portal vein thrombosis after S&GD.

Portaprival collaterals were more evident after DSRS (91%) compared to S&GD (65%). The high incidence and the unique patterns of these collaterals after DSRS are initiated by the high-pressure gradient between the portomesenteric and gastrosplenic compartments. With S&GD the high pressure in the portomesenteric axis and splenic stump triggers the formation of new collaterals in the natural portogastric pathways.

Preservation of hepatocyte functions is a major determinant of long-term surgical outcome. The significant changes in some of the conventional biochemical tests on long-term follow-up may reflect late impairment of hepatocellular functions after both procedures. Analysis of this data after being stratified according to the type of hepatic disease linked the documented enzymatic changes after S&GD to the cirrhotic and mixed population.

The phenomenon of chronic hyperbilirubinemia in the schistosomal patients after DSRS has been further substantiated in this report.^{37,40,44,48} The significant reduction in total bilirubin in the same population after S&GD may

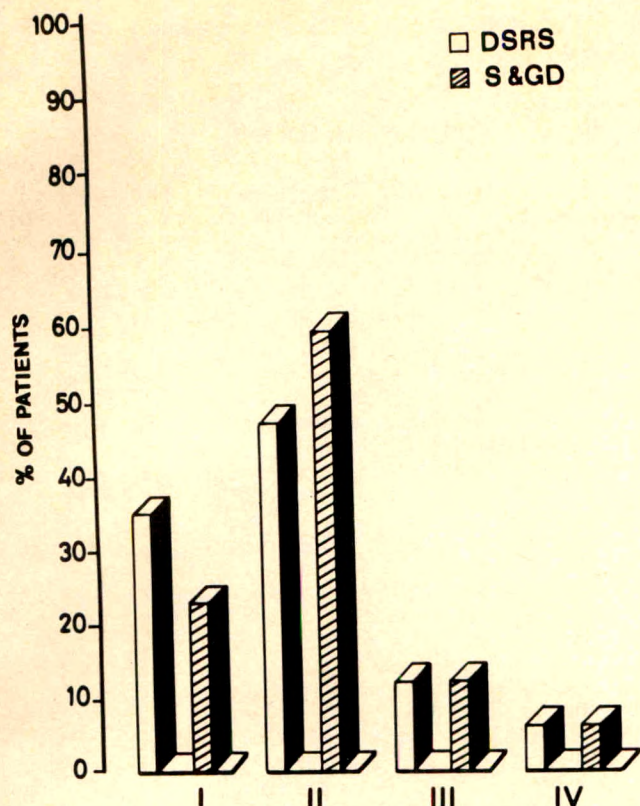


FIG. 4. The incidence of portal perfusion grades after DSRS and S&GD. Both DSRS and S&GD maintained portal perfusion in 94% of patients with more grade I after DSRS and II after S&GD.

be explained by interruption of the associated hyperdynamic splenic circulation with elimination of the hemolytic effect of the turbulent sinusoidal flow.^{37,40}

Ascites was clinically detected with similar incidence among survivors of both procedures. The temporary ascitogenic effect of extensive dissection with lymphatic interruption may explain the higher rate of early postoperative ascites after DSRS.

The present study showed a similar cumulative rate of total population long-term survival after DSRS and S&GD, despite the higher rebleeding rate after S&GD. This data clarifies the encouraging benefits and dictates the absolute necessity of sclerotherapy for S&GD rebleeders. It further underscores the impact of chronic hepatic disease on patient survival by documenting similar incidences of liver cell failure after both procedures.

The quality of survival after surgical management of variceal hemorrhage is essentially determined by the development of encephalopathy. Despite the potential hemodynamic and metabolic advantages of both modalities, the total incidence of encephalopathy was significantly higher after DSRS (18.7%) compared to S&GD (7.3%). Interestingly such a statistical difference was not detectable among survivors because of the concomitant hepatocel-

lular dysfunction and the subsequent high attrition rate of the encephalopathic patients after DSRS. With the hemodynamic stability of S&GD patients, the risk of postoperative encephalopathy may be mainly endogenous and largely determined by the natural course of the underlying chronic hepatic disease.

Long-term survival of variceal bleeders is concurrently modulated by the therapeutic efficacy of the implemented procedure and the concomitant chronic liver disease. Very few reports have addressed this interrelationship with DSRS.^{48,77,80,81} The better long-term survival of the schistosomal population after DSRS (90%) compared to S&GD (75%) documents the advantage of the higher efficacy rate of selective shunt in protecting patients with preserved hepatocyte functions against variceal hemorrhage. Because of the physiologic advantages of DSRS and S&GD, the schistosomal patients were less prone to develop encephalopathy after both procedures.

The cirrhotic and mixed population showed similar survival rates after DSRS (73%) and S&GD (72%), with a significant higher incidence of variceal hemorrhage after S&GD (38%) and encephalopathy after DSRS (27%). These findings reflect the deleterious effects of the progressive cirrhotic process on the intrahepatic vascular block and functional hepatic reserve.

For valid comparison with similar trials, the available data from different centers must be carefully reviewed and critically analyzed; first because of the worldwide existence of unavoidable epidemiologic and socioeconomic factors that magnify the etiologic spectrum of portal hypertension, and second due to the unlimited continuous efforts to add new techniques to the nonshunt procedures.^{23,82}

Although DSRS has been carefully evaluated, few reports have focussed on S&GD.^{43,44,59} Professor Hassab,⁵⁹ who advocated our adopted technique, has published the largest known series of S&GD without esophageal transection. With a follow-up of 5 to 10 years, he reported a 10% incidence of operative deaths, 10% rebleeding rate, 4% ascites, and 18% total mortality. However the present report and most of the western publications showed a higher rate of recurrent hemorrhage and lower cumulative survival rate.²³ These variable results may be related to the discrepancy in patient populations and periods of follow-up.

The only available randomized study that includes DSRS and S&GD was conducted in the schistosomal population by the Brazilian group.⁴⁴ The 2-year follow-up report showed a similar rebleeding rate after DSRS (13.3%) and S&GD (12.9), with detection of encephalopathy in 6.9% of the first group.

In a similar nonrandomized study, but with 67% alcoholic cirrhosis, Rikkers et al.⁴³ cited a 5-year survival rate of 40% after DSRS and 75% after S&GD. Variceal

hemorrhage recurred in 8% and 50% of each group, respectively. Encephalopathy developed after both procedures, with an incidence of 12% (DSRS) and 13% (S&GD). The prohibitive high rebleeding rate after S&GD and the low cumulative survival rate after DSRS in Rikker's report can be attributed to the progressive nature of alcoholic cirrhosis.

The considerable rebleeding rate after S&GD in our study and other publications emphasizes the potential advantages of adding esophageal transection to completely interrupt the intraesophageal venous plexus. This is further supported by the current results of the Sugiura procedure and its modifications.⁸³⁻⁸⁵ However adjuvant sclerotherapy for variceal rebleeders may be a good alternative policy to adopt with S&GD. The need for prophylactic sclerosis is equivocal and a clinical trial is required to draw solid recommendations.

Therapies are always technically demanding and require sufficient experience. Surgeons seeing a limited number of variceal bleeders may find the nonshunt procedures technically easier and faster to perform than DSRS. Based on the current results and the previously published series, the authors believe that this fact does not justify the routine use of nonshunt surgery, especially in patients with excellent hepatic reserve and suitable venous anatomy.

In conclusion, in the present series, management of Child A/B variceal bleeders by DSRS and S&GD achieves low operative mortality with higher rates of variceal rebleeding after S&GD (27%) and encephalopathy after DSRS (18.7%). Both surgical procedures have similar cumulative survival for total population, with rates of 80% and 79%, respectively. Endosclerosis was an adjuvant therapy for rebleeding in 23% of S&GD patients.

This clinical trial shows that selective shunt has better results in the schistosomal patients compared to S&GD. The risks of variceal rebleeding and encephalopathy were acceptable (10%) with 15% survival advantages. With the cirrhotic and mixed population, both procedures provide similar opportunity for long-term survival (DSRS 73%, S&GD 72%), with higher incidence of rebleeding after S&GD (38%) and encephalopathy after DSRS (27%).

Recently three different prospective randomized trials proved the efficacy of sclerotherapy as a good alternative to DSRS for initial and definitive management of variceal bleeding in the cirrhotic population.⁸⁶⁻⁸⁸ For the schistosomal and nonalcoholic cirrhotics, a similar study with the addition of S&GD as a third proposed treatment method is mandatory for dictating the optimal therapeutic modality currently available for management of these patients. This data proves the superiority of DSRS in management of schistosomal variceal bleeders and verifies the alternative role of S&GD backed up by sclerotherapy in

the cirrhotic and mixed population, especially those with marginal hepatic reserve.

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Acute Pancreatitis at Its Centenary

The Contribution of Reginald Fitz

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1989 represents the 100th anniversary of Reginald Fitz's initial characterization of acute pancreatitis. Our current understanding of this disease has advanced little beyond Fitz's early description. While survival from pancreatitis has improved largely through advancements in critical care techniques, no medical or surgical therapy exists that can limit pancreatic autodigestion and inflammation. Recent investigations have suggested that pancreatitis may result from a disruption of normal stimulus-secretion coupling within the acinar cell. Future research based on these observations may ultimately result in successful therapy for this disease.

ONE HUNDRED YEARS ago, Reginald Fitz of Boston provided the first accurate description of acute pancreatitis. The centenary of this event provides an opportunity to review Fitz's accomplishment, as well as to consider the current status of this disease.

Fitz was born in Chelsea, Massachusetts on May 5, 1843. His preliminary education took place at the Chauncy Hall School in Boston, where his work was of no particular distinction. With little enthusiasm he entered Harvard College in 1858. Initially disappointed with his education at Harvard, Fitz left college during his junior year to begin work in a Michigan copper mine. This experience apparently instilled in him a new desire for the academic life. Fitz wrote to his family, 'I find that it will be much pleasanter to become a professional man and live moderately and free from care than to become rich and have my mind continually harassed with care and anxiety.'¹ He returned to Harvard in 1862.

Fitz's subsequent education proceeded without interruption. At Harvard he received a B.A. degree in 1864 and a M.D. degree in 1868. After earning his medical degree, Fitz began a period of training in Europe that was to prove critical to his later work. Studying first in Vienna,

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Fitz acquired an intense blend of pathologic and clinical knowledge under the guidance of Rokitsansky and Skoda. In so doing he became expert in detailed postmortem examination and clinical diagnosis. In addition he was exposed to Theodor Billroth, then at the zenith of his career.^{2,3} This interaction may explain the uniquely surgical approach that Fitz brought to his later work.

Fitz subsequently left Vienna for Berlin, where he joined the new school of pathology founded by Virchow. It was Virchow who first conceived the notion of cellular pathology,⁴ in which disease is considered not an independent entity, but rather an aberration of normal cellular function. Integral to this new formulation were many technical advances that allowed for the study of diseased tissues by means other than simple visual inspection. While working in the laboratory of Virchow, Fitz became expert in microscopy. When, in 1870, he returned to Boston as one of the first of Virchow's students in the United States, he introduced both new technical skills and innovative ideas regarding the cell as the essential component of disease.

Fitz was appointed Microscopist at the Massachusetts General Hospital and Instructor in Pathologic Anatomy at the Harvard Medical School. In these positions he disseminated the theories of Virchow and provided instruction in the microscopic examination of tissues. Fitz proved extremely industrious, compiling large volumes of autopsy data that formed the basis for many of his later writings. In 1873 he was appointed Assistant Professor of Pathology; in 1878 he was appointed Shattuck Professor of Pathologic Anatomy. In 1892, at the age of 49, he was named the

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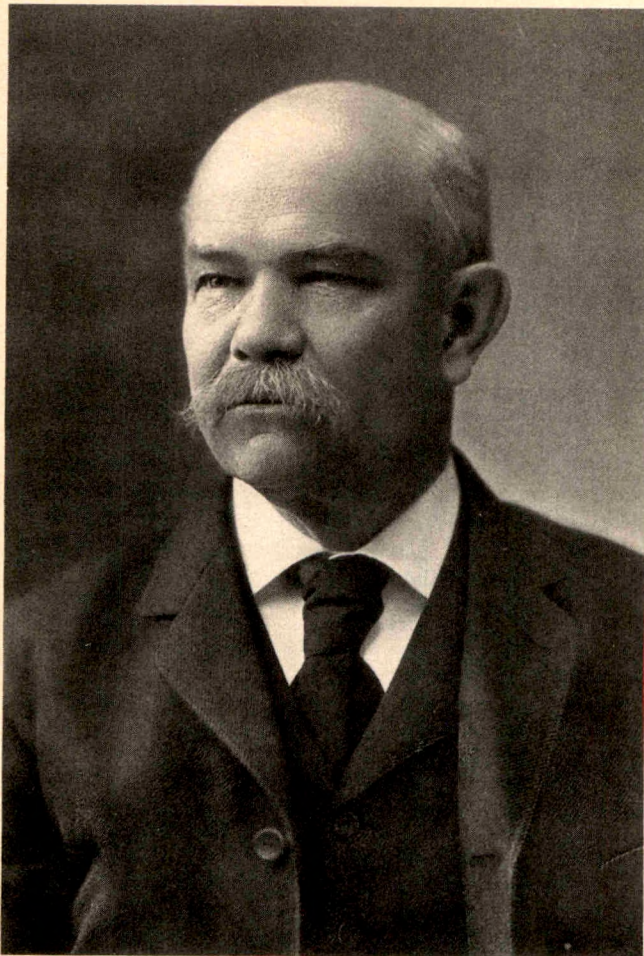


FIG. 1. Reginald Huber Fitz circa 1910. Reproduced with permission, Yale University Medical History Library, New Haven, CT.

Hersey Professor of the Theory and Practice of Physic (Fig. 1).

Throughout his career Fitz demonstrated a strong commitment to medical education. He chaired the curriculum committee at the Harvard Medical School for 17 years. A talented teacher, Fitz was noted for his demanding lectures in which critical information was transmitted eloquently, logically, and accurately. The surgeon John Blake recalled that 'he had a habit of tilting his head backward, closing his eyes, talking with extreme rapidity and fluency, never missing a word, for 61 minutes in the hour . . . it was as if he read a carefully prepared lecture from the inside of his eyelids.'⁵

In addition to his interests in cellular pathology and medical education, Fitz retained a tenacious interest in bedside clinical medicine. It was in this arena that Fitz's surgical inclinations became apparent. As a pathologist at the Massachusetts General Hospital, he was known for his preoperative visits to patients on the surgical wards who were to undergo laparotomy. He was incessant in his attempts to correlate clinical findings with subsequent

pathologic information, and was frequently outspoken in his opinion regarding preoperative diagnosis. These practices may have initiated some rancor among his more cautious clinical colleagues. Indeed it required 2 years of heated correspondence before Fitz was allowed Visiting Physician privileges at the MGH in 1887.¹ Using these privileges, however, Fitz was able to carry on an active clinical practice in addition to his work in pathology. Using the skills imparted to him by Rokitansky, Skoda, and Virchow, Fitz integrated histologic and bedside diagnosis in a manner that allowed unprecedented progress in the clarification of surgical pathology.

Fitz's contribution toward the elucidation of acute abdominal pathology was enormous. Although best known for his characterization of acute appendicitis,⁶ Fitz also provided landmark descriptions of intestinal obstruction⁷ and of the complications arising from Meckel's diverticulum.⁸ In each instance Fitz painstakingly analyzed a large group of carefully selected patients to delineate the salient features of clinical presentation, natural history, and pathology. In this regard he was both explicit and succinct, as demonstrated by his conclusions regarding appendicitis: 'the vital importance of the early recognition of perforating appendicitis is unmistakable. Its diagnosis, in most cases, is comparatively easy. Its eventual treatment by laparotomy is generally indispensable. Urgent symptoms demand immediate exposure of the perforated appendix, after recovery from shock, and its treatment according to surgical principles.'⁶

Fitz's contribution to the modern concept of acute pancreatitis was no less important. Read before the New York Pathological Society as the Middleton-Goldsmith Lecture, his paper entitled 'Acute Pancreatitis: A Consideration of Pancreatic Hemorrhage, Hemorrhagic, Suppurative, and Gangrenous Pancreatitis, and of Disseminated Fat-Necrosis' was published in the *Boston Medical and Surgical Journal* on February 21, 1889⁹ (Fig. 2). While previous authors including Aubert,¹⁰ Classen,¹¹ Friedrich,¹² and Senn¹³ had all provided anecdotal reports of acute pancreatitis and its complications, it was Fitz who provided the first systematic analysis of this disease.

In his paper Fitz presented 53 patients with pathologically documented acute pancreatitis. Clinical details, including the presence or absence of abdominal pain, nausea, anorexia, fever, jaundice, and the findings on abdominal examination are extensively reviewed. In addition Fitz reported the pathologic findings that allowed him to distinguish the hemorrhagic, suppurative, and gangrenous forms of the disease. Etiologic factors including gallstones, alcohol, perforating gastric ulcer, and trauma are all mentioned. Fitz also stressed important points regarding differential diagnosis, particularly with respect to intestinal obstruction. He described pancreatic abscess and splenic vein thrombosis, as well as an apparent pancreatic pseu-

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BOSTON MEDICAL A.

Original Articles.**ACUTE PANCREATITIS.****A CONSIDERATION OF PANCREATIC HEMORRHAGE,
HEMORRHAGIC, SUPPURATIVE, AND GAN-
GRENOUS PANCREATITIS, AND OF
DISSEMINATED FAT-NECROSIS.¹****BY REGINALD H. FITZ, M.D.,***Shattuck Professor of Pathological Anatomy in Harvard University
and Physician to the Massachusetts General Hospital.***UNTIL the time of Clässen² the evidence of an**FIG. 2. Title page of Fitz's initial paper on pancreatitis, published on February 21, 1889 in the *Boston Medical and Surgical Journal*.

docyst. Fitz further suggested a causal relationship between pancreatitis and disseminated fat necrosis, and provided the first clear link between pancreatic hemorrhage and pancreatitis. In light of these progressive observations, Fitz's extraordinary claim that 'the dark-brown pancreas may lie nearly free in the omental cavity [and] . . . may be discharged as a slough from the bowels' may be easily disregarded.

On the basis of his exhaustive review, Fitz concluded 'Acute inflammation of the pancreas is both a well characterized disease, and one which is much more frequent than is generally thought. It is an important cause of peritonitis, and one readily overlooked.' In contrast to his recommendations of prompt laparotomy in acute appendicitis, Fitz observes that 'an operation . . . in the early stages of this disease, is extremely hazardous.' It is interesting to note that Fitz subsequently waived from this conservative stance. Thus in 1903 he proposed that 'In cases of acute pancreatitis . . . laparotomy in an increasing number of cases has proven the most satisfactory method of treatment, and, like most abdominal operations for the relief of acute symptoms, is the more helpful the earlier in the course of the disease it is performed.'¹⁴

The impact of Fitz's 1889 treatise was clear. For the first time the varied manifestations of acute pancreatitis were organized into a systematic framework that allowed

for its eventual antemortem diagnosis. In 1913 the surgeon W. W. Keen from Philadelphia wrote, 'In another fruitful field, pancreatitis, [Fitz] laid the foundations of our present knowledge of the pathology and symptomatology and therefore, of the correct treatment of this so frequently and suddenly fatal disease.'¹⁵ Fitz's work contributed greatly to the progress of other turn-of-the-century investigators, including Opie in the field of gallstone pancreatitis,¹⁶ and Mayo-Robson in the arena of surgical therapy.¹⁷ Thus Fitz's contributions to the subject of pancreatitis were recognized for their breadth and vision even before his death in 1913. Given his primary role in the description of pancreatitis, it is ironic that Fitz's death was related to another autodigestive phenomenon: he died after hemorrhage from a gastric ulcer.³

In the immediate years following Fitz's death, several other physicians provided significant contributions regarding the pathophysiology and diagnosis of acute pancreatitis. Of particular significance were Moynihan's further delineation of the surgical approach to pancreatitis in 1925,¹⁸ and the demonstration of elevated serum amylase levels by Elman, Arneson, and Graham in 1929.¹⁹

In considering the current status of acute pancreatitis, it is particularly distressing that Fitz's comments, now 100 years old, continue to approximate our current understanding of this disease. Fitz's classifications of hem-

orrhagic, suppurative, and necrotizing pancreatitis persist, despite minimal understanding of the basis for these diverse presentations. Similarly, while much knowledge has been gained regarding the etiologic factors suggested by Fitz, the precise means by which these diverse elements all induce pancreatitis remain unclear.

Particularly in the area of therapy, little progress has been made. While mortality rates have doubtlessly improved largely through the advance of critical care techniques,²⁰ there has been no significant progress toward the development of specific therapies capable of limiting pancreatic inflammation and autodigestion.²¹ Thus care of the patient with acute pancreatitis remains largely custodial, with attention toward maintaining adequate circulatory volume, maximizing renal perfusion, supporting respiration, and providing adequate nutrition. Attempts to 'put the pancreas at rest' by inhibiting acinar cell secretion with regimens involving nasogastric suction,²² cimetidine,²³ atropine,²⁴ glucagon,²⁵ calcitonin,²⁶ and somatostatin²⁷ have met with almost uniformly disappointing results. Inhibitors of proteolytic enzymes, including aprotinin (Trasylol) have similarly been ineffective in ameliorating the disease.²⁸ Endoscopic retrograde cholangiopancreatography and endoscopic papillotomy may be useful in preventing the need for laparotomy during the period of acute illness,²⁹ but their potential to alter the progression of pancreatitis has been evaluated only recently.³⁰ As for surgical therapy, the principles of lesser sac debridement and drainage enunciated by Moynihan in 1925 remain very nearly the state of the art,^{31,32} and Fitz's confusion regarding the timing of surgical intervention persists as controversy in the current surgical debate.^{33,34} While most patients with acute pancreatitis will recover spontaneously regardless of therapy, 10% to 15% continue to exhibit a fulminant course characterized by many complications and substantial mortality.³⁵

In this setting perhaps it would be advisable to recall that Fitz's progress in clarifying acute pancreatitis was to a large extent dependent on the principles of cellular pathology as delineated by Virchow. While most subsequent investigations have addressed the pathophysiology of pancreatitis at the whole-organ level, it has recently become clear that the initiating events in pancreatitis may need to be evaluated at the level of the acinar cell itself. Specifically recent investigations using several experimental models of acute pancreatitis have suggested that a disruption in acinar cell stimulus-secretion coupling may play a critical role in initiating the disease. Thus in several *in vivo* models of pancreatitis,³⁶ as well as an *in vitro* model recently developed in our laboratory,³⁷ an apparent blockade to zymogen granule exocytosis occurs within the acinar cell. Subsequently accumulated zymogen granules undergo abnormal fusion with lysosomes, a process known as crinophagy.³⁸ Of note the lysosomal enzyme

cathepsin B is capable of activating trypsinogen.³⁹ Thus a potential mechanism exists by which a disruption in normal stimulus-secretion coupling within the acinar cell may lead to intracellular zymogen activation and pancreatic autodigestion.

In the future more rational attempts at specific therapies in acute pancreatitis may be directed toward the inhibition of lysosomal enzyme activity⁴⁰ or the restoration of normal stimulus-secretion coupling within the acinar cell. In addition the selective inhibition of zymogen protein synthesis also may prove beneficial by limiting the amount of zymogen protein available for intracellular activation. In this regard our laboratory recently has demonstrated a beneficial effect of cholecystokinin receptor blockade in several experimental models of acute pancreatitis.⁴¹

It is a cause for concern that the status of acute pancreatitis today remains disappointingly similar to Fitz's 100-year-old description. It seems clear, however, that investigation of acute pancreatitis at the level of the acinar cell itself may allow more rapid progress to be made. Fitz's contribution was based in large part on 19th century principles of cellular pathology; recent scientific progress permits investigation of the intracellular mechanisms that result in pancreatitis. Manipulation of these mechanisms ultimately may provide the basis for rational therapeutic intervention. Indeed, current scientific developments may enable the development of specific cellular therapies for acute pancreatitis and provide for a more promising second century in our understanding of this disease.

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BOOK REVIEWS

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Swenson's Pediatric Surgery (5th Edition). John G. Raffensperger. 978 pp. East Norwalk, CT: Appleton & Lange, 1989. \$145.00

THIS 5TH EDITION OF *Swenson's Pediatric Surgery* provides a 10-year update with many new authors. Editor Dr. John Raffensperger has compiled a thorough introductory text encompassing the major disorders encountered in General and Thoracic Pediatric Surgery. Pediatric urology, although a major area of pediatric surgery, is not covered in the text.

The authors have used a problem-oriented approach to reflect the actual presentation of the pediatric patient. The text is, therefore, of particular interest as a resource for students, surgical residents, and general surgeons. The approach to the evaluation and management of the child with a surgical condition with emphasis on a humanistic approach and the important aspects of critical care are presented particularly well, with almost 15% of the text devoted to fundamentals of pediatric surgery.

Although the volume covers the broad principals of diagnosis and surgical treatment of most disorders of infancy and childhood, many of the details of management and controversies are included superficially. Specifically chapters concerned with diaphragmatic hernia, exstrophy, and the adrenal glands do not cover broad perspective of the disorders. Several chapters include extensive discussion with respect to surgical techniques used by the authors with very superficial presentation of other methods, although they may be widely used by other pediatric surgeons. The chapters on Hirschsprung's disease, imperforate anus, and inflammatory bowel disease are noteworthy in this respect.

The illustrations supplement the text well and are of good quality. Because the volume is not a definitive reference text and is primarily oriented to the physician who is not a trained pediatric surgeon, it would be appropriate to have a paperback edition.

ERIC W. FONKALSRUD, M.D.
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Aortic Surgery. John J. Bergan and James S. T. Yao. 574 pp. London: WB Saunders, 1989. \$66.00.

AORTIC SURGERY IS ANOTHER outstanding contribution by Drs. Bergan and Yao based on their Annual Vascular Symposium in Chicago in December. By assembling many of the world leaders, it has been possible to compile a current update on aortic surgery and many interesting and challenging associated considerations. Dr. Wiley Barker provides an historical perspective of surgery of the aorta that is informative and interesting. The table of contents is organized to provide rapid review of specific aspects ranging from patient evaluation to specific op-

erative intervention for both thoracoabdominal lesions and aortic aneurysms at all levels. Other sections address the problems of concomitant aortic and other surgical procedures, alternative aortic surgical procedures, and pediatric aortic surgery. Complications associated with aortic surgery are reviewed in detail.

Despite multiple authorship, the editors have maintained appropriate organization of the material. The figures selected are of excellent quality and compliment the text appropriately. Additional references at the end of each chapter provide further resource material selected by experts. To compliment the outstanding scientific quality of this material, the publisher has maintained the usual outstanding quality of cover, paper, and print at a reasonable cost in today's market. This important contribution should be in the personal library of any surgeon or physician dealing with aortic pathology.

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Complications in Surgery and Trauma (2nd Edition). Lazar J. Greenfield. 1064 pp. Philadelphia: JB Lippincott, 1989. \$95.00.

A PROSPECTIVE READER IS first met by the falling dominoes depicted on the cover of *Complications in Surgery and Trauma, Second Edition*, edited by Lazar J. Greenfield, with 74 contributors, 40 of whom are from either the University of Michigan or the Medical College of Virginia. The red falling dominoes reflect problems surgeons encounter once complications begin to occur.

From my assessment the title is misleading. Although many of the chapters focus on perioperative or post-traumatic complications, much of the dialogue focuses on complications of disease processes or secondary to nonoperative conditions. In fact this text covers complications encountered by the surgeon or any physician treating patients with surgical problems, including trauma, endocrine, gastrointestinal, thoracic, vascular, pediatric, transplantation, and others. The phrase 'and Trauma' applied to the title and various chapters is somewhat redundant. If trauma was to have been a major focus, other chapter titles could have been selected.

The text has 10 major divisions, rather arbitrarily organized:

1. Complications of Wound Healing and Breast and Plastic Surgery
2. Systemic Complications and Trauma
3. Complications in Thoracic Surgery and Trauma
4. Complications in Cardiovascular Surgery and Trauma
5. Complications in Alimentary Tract Surgery and Trauma
6. Complications in Endocrine System Surgery
7. Complications in Nervous System Surgery and Trauma
8. Complications of Genitourinary Surgery and Trauma

9. Complications in Musculoskeletal Surgery and Trauma
10. Incidence of Complications

The table of contents lists the chapter subdivisions, which make consulting the index unnecessary.

Although the chapters contain material easy to locate for either spot or detailed reading, the writing style is inconsistent. The book would profit from a consistent approach to writing and/or editing style. Some chapters are pointedly and succinctly written and contain helpful directed references. Other chapters are encyclopaedic and exhaustively cover the subject with many references (in excess of 150 citations), some of which are not classics. Some chapters are richly illustrated and others are mainly text. Some of the illustrations could profit from being redrawn because they are reproductions of material seen frequently by the reader.

This second edition contains new material and new authors, while some chapters have been relatively unaltered from the first edition. In the time between editions, new controversies, complications, and nonmedical problems have continued to plague the surgeon. Examples of missing complications are atrioventricular separation following mitral valve surgery and cardiac shunts, and fistulas following penetrating cardiac trauma, neither of which is covered in the chapter on Cardiac Surgery and Trauma. Such complications are specialty specific and are usually covered in the specialty texts. Except for medical audits briefly covered on page 911, the complications of trauma center closures, the Medicare demerit system for discovered complications (under the Third Scope of Work), other 'system' complications, medical legal harassment, and economic imbalances are not mentioned and would be deserving of page print in a text of this magnitude.

Although there are complications that are 'missing' from the text, it should be available reading for surgical students, residents, fellows, and practitioners, as well as other specialists who participate in the care of surgical patients.

A book in its second edition so soon after the publication of the first edition obviously was extremely successful in its first printing. This second edition builds on the strengths of the first. I recommend that this book be added to every surgeon's library.

KENNETH L. MATTOX, M.D.
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Controversies in the Management of Venous Disorders. Bo Eklof, Jan Erik Gjores, Olav Thulesius, and David Bergqvist. 328 pp. Stoneham, MA: Butterworths, 1989. \$185.00.

THE EDITORS, AND MOST of the authors of individual chapters, are Scandinavians and the work reviews the tremendous contributions they have made in understanding the pathophysiology of venous disorders and the major advances now available for medical and surgical treatment. These authors present the most up-to-date compilation of knowledge on venous disorders. In addition invited commentary by world-renowned clinicians from other countries provides a unique balance to the presentation of the Scandinavian experience and tremendously adds to the overall value of this book.

The chapters on physiology and pathophysiology of venous disorders of the leg are concise and well written. They provide an excellent basis for the subsequent chapters that discuss clinical and laboratory techniques for diagnosis and measurement of

the extent of venous disorders. Chapters include detailed discussions of both medical and surgical treatment of acute and chronic venous disorders with concise and well-documented rationale for selecting one form of treatment over others.

Of particular interest in this book are some of the unique chapters not always found in a text of this type. These include chapters on 'economical aspects of treatment of varicose veins' and 'epidemiology of deep venous insufficiency.'

In all this book provides an excellent resource for surgeons and internists alike who may be involved in the management of venous disorders of all types. I consider it an invaluable addition to the physician's ready reference library.

LARRY H. HOLLIER, M.D.
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Microsurgical Tissue Transplantation. Riediger and M. Ehrenfeld. 243 pp. Chicago: Quintessence Publishing Co., Inc., 1989. \$48.00.

THE TEXT MICROSURGICAL TISSUE TRANSPLANTATION, edited by Professor Dr. D. Riediger of Stuttgart and Dr. M. Ehrenfeld of Tübingen, West Germany, is a compilation of many of the papers presented at the International Symposium on Microsurgical Tissue Transplantation in Tübingen, Federal Republic of Germany, November 27 to 29, 1987. The meeting, as well as the edited text, reflects the state of the art in reconstructed microsurgery as practiced in 1987 in Europe and specifically in West Germany.

Part I, Microsurgery of the Head and Neck Region, is a series of papers demonstrating the many advantages of both soft-tissue and osseous reconstruction with vascularized composite tissue following extirpation of tumor, disease, or trauma. The radial forearm flap is extolled for its virtues in intraoral reconstruction. Mandibular reconstruction is accomplished with vascularized iliac crest segments. Integrated osseous implants are used to permit fixation of intraoral prosthetic appliances enhancing both mastication as well as improving the overall aesthetic result. Contour defects in the head and neck region are reconstructed with various adipose flaps or omentum. Part III, Microsurgery of the Oropharyngeal Region, deals with cervical esophageal reconstruction using vascularized jejunum. Both part I and II account for approximately one half of the entire text.

Part III, Microsurgery of the Trunk and Extremities, summarizes the results of muscle transplantation, wound coverage, revascularization, and replantation. This section is rather short, consisting only of 45 pages.

Part IV, Microsurgery, is also a rather short section consisting of only 42 pages. Its strength resides in the excellent discussion by Hano Milleli on the current state of peripheral microsurgery. Other chapters reflect various contributions in microsurgery, specifically in the head and neck region.

Part V, Basic or Scientific Research, reflects a series of papers dealing with approved techniques in microvascular surgery, the use of allografts in tissue transplantation, and various methods to monitor tissue transplants.

The strength of the text resides in depicting the state of the art in microneural reconstruction particularly in the head and neck region as practiced in Europe in 1987. A variety of difficult clinical problems are presented. Reconstruction is accomplished with various types of composite tissue using the microsurgical method.

As one would expect, the text suffers from various problems that one encounters when editing various manuscripts from an international meeting. Manuscripts may not be received in a timely fashion or when received they often reflect a rather hurried manuscript submitted after the presentation, often with less enthusiasm. Furthermore, in an effort to be encyclopedic, contributions in many parts are deficient. This is especially noted in the extremity and the basic science sections.

The textbook does reflect the excellent quality of papers presented at the International Symposium on Microsurgical Composite Tissue Transplantation in Tübingen in 1987. The papers reflect recent advances and contributions, primarily by the European authors in head and neck reconstruction. The editors are to be congratulated for compiling this material as well as their own important individual contributions.

DONALD SERAFIN, M.D.
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Current Critical Problems in Vascular Surgery. Frank J. Veith. 587 pp. St. Louis: Quality Medical Publishing, Inc., 1989. \$69.95.

THIS CONCISE BOOK IS a direct outgrowth of the popular Annual Symposium on Current Critical Problems and New Horizons in Vascular Surgery organized by Dr. Frank Veith and his colleagues at the Montefiore Medical Center and Albert Einstein College of Medicine. It is one of several texts that are currently being published to summarize surgical symposia and to distribute their content to surgeons who cannot attend the meetings but who are interested in keeping abreast of medical research. This particular volume contains selected material from the 1987 and 1988 symposia.

The purpose of this book is to present a brief summary and critical analysis of all major topics in arterial, venous, and lymphatic diseases. Herein lies the strength of this work: an exhaustive but truly concise review of vascular surgery presented by more than 150 leading vascular surgeons who have presented the material at the meetings. In several major sections, the authors comment on important issues in vascular surgery manpower, lower-extremity ischemia, reoperative arterial reconstructions, venous disease, endovascular diagnostic and therapeutic techniques, arterial aneurysms, aortoiliac arterial occlusive disease, experimental advances, preoperative and intraoperative management, and finally, controversies in carotid surgery. Although a few chapters may be too concise, the majority are clear statements of current knowledge with a pertinent selection of recent references. The illustrations emphasize key concepts, and tables and graphs provide a quick means of grasping important facts. The material is fresh, very readable, and interspersed with judicious comments and recommendations from the experts.

Perhaps the main value of this excellent book is a ready reference for young surgeons who are preparing for certification examinations. For more experienced surgeons, the book provides a condensed review of the essential material that supports current vascular surgery practice and provides a provocative look at new horizons in the field. For its content and its cost, *Current Critical Problems in Vascular Surgery* is a true bargain in continuing medical education and is highly recommended.

JOHN W. HALLETT, JR., M.D.
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Echocardiography and Doppler in Cardiac Surgery. Gerald Maurer and Werner Mohl. 355 pp. New York: Igaku-Shoin Medical Publishers, Inc, 1989. \$97.50.

THE DEVELOPMENT OF TWO-DIMENSIONAL echocardiography, Doppler echocardiography, and color flow Doppler echocardiography has revolutionized the 'noninvasive' demonstration of cardiac surgical anatomy and physiology. The introduction of transesophageal probes capable of all these ultrasound modalities has permitted its increasing use in the cardiac operating room and has succeeded in coordinating the diagnostic acumen of cardiologist, anesthesiologist, and cardiac surgeon in that setting.

This book succeeds in presenting the most relevant aspects of diagnostic ultrasound in a collection of 21 chapters. These cover the basic principles of echocardiography, Doppler, and color flow Doppler, as well as consideration of the preoperative, intraoperative, and postoperative evaluation of virtually all significant disease states encountered by the practicing cardiac surgeon. Therapeutic applications of ultrasound are mentioned in a single chapter.

As with all multiply authored textbooks, there is a certain degree of repetition that could be avoided. This does not detract from the work, particularly in that individual chapters stand alone well. The work is extremely well illustrated. All the contributors are well recognized experts in their field (which is frequently surgery). The information that each provides is clearly comprehensive, well referenced, and does not differ significantly in content from material delivered at national and international meetings on the subject of echocardiography in cardiac surgery delivered by these same authors. As such this book succeeds in presenting a state of the description of the entitled subject.

This book is recommended for all surgeons, anesthesiologists, and cardiologists who are interested in intraoperative ultrasound applications as well as for residents in training in these areas. As in any rapidly changing field, it is likely that technological changes will result in some of the material now considered to be research being either widely applied or falling into disfavor. In addition it is quite clear that the interpretation of ultrasound data requires a great deal of clinical experience and specialized training, which is not available in a formal way. This book serves as a useful introduction to the great potential of echocardiography in cardiac surgery and properly serves as an introduction and a point of departure for its practitioners.

PETER K. SMITH, M.D.
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Vascular Surgical Techniques: An Atlas (2nd Edition). Roger M. Greenhalgh. 448 pp. Philadelphia: WB Saunders, 1989. \$165.00.

AS IN OTHER FIELDS of surgery, there is no single, right way to perform most vascular operations. Nuances in approach, choices in vascular grafts, and variations in technique permit a wide range of performance within the limits of accepted practice. This variability, together with the fact that vascular procedures are well suited to schematic illustration, has resulted in the publication of a number of atlases of vascular surgery over the past two decades. This atlas, in its second edition, is of high quality and should be especially useful to surgical trainees and young practitioners because it provides a resource for review of the essential steps in a large number of operative procedures, in-

cluding some of the newer endovascular techniques. The editor, Roger M. Greenhalgh, has carefully selected expert contributors from around the world, presenting material by 84 authors from 12 different countries, each of whom describes with diagrams and text his or her personal approach to a given vascular problem. Despite multiple authorship, there is surprisingly little repetition or contradiction. Most procedures included are fully consistent with accepted surgical practice. A few, however, are of questionable value or should be considered experimental, but unfortunately, there are no editorial comments to alert the novice to the unproved techniques. While the artwork throughout this compiled atlas is generally of good quality, it varies considerably in style from one chapter to the next. Undoubtedly the final

product would have been enhanced if all illustrations had been done by a single artist. The book would also be strengthened by the addition of an index because the table of contents is not sufficiently detailed to allow the reader to find such common procedures as lumbar sympathectomy and lower extremity fasciotomy. Editorial mistakes are infrequent, but improperly oriented illustrations, incorrect figure legends, and some typographic errors may distract the more discerning reader. These criticisms notwithstanding, the work is a worthy contribution to the ever-enlarging library of excellent vascular surgical texts.

ROBERT B. SMITH III, M.D.
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LETTERS TO THE EDITOR

September 20, 1989

Dear Editor:

In their article regarding wounds of the colon and their treatment, George and colleagues.¹ refer to war wounds caused by high-velocity missiles and shrapnel. Certainly the missiles referred to as shrapnel should be labeled high-explosive fragments. A letter I have written,² with the replies of two authors regarding the proper terminology for missiles, is readily available to the interested surgeon. Data regarding the percentage of wounds caused by the various missiles are included in the letter.

The error in describing shrapnel has entered standard dictionaries. Webster's Collegiate Dictionary (1946)³ gives the proper definition with an illustration of the shell enclosing the balls; I have seen this same illustration in a multivolume dictionary from the 19 century. Webster's New World Dictionary (1970)⁴ also includes the erroneous statement that any fragment of an exploding shell is shrapnel.

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GEORGE N. J. SOMMER, JR., M.D.
Trenton, New Jersey

October 30, 1989

Dear Editor:

The authors appreciate Dr. Sommer's attempts to point out the original definition of 'shrapnel.' He has reported¹ that the Germans in World War II referred to steel balls, which were enclosed in the explosive casings of land mines, as shrapnel, this also being the definition in Webster's Collegiate Dictionary of that era.²

However, to place this in accurate historical context, I would like to point out that shrapnel was originally developed by British Lieutenant Henry Shrapnel (1761 to 1842).³ It was an artillery shell containing a number of balls and powder that burst the shell and was first used by the British in Surinam in 1804. This particularly devastating weapon was used extensively against infantry in one of the bloodiest wars humankind has witnessed: the American Civil War. It was referred to as 'grape shot and canister' during that conflict. Since World War II, the term 'shrapnel' has been used to refer to the fragments of the shell casing thrust by an explosive charge.

The point is well taken that we should be precise in defining the mechanisms of injury so appropriate comparisons can be made and correct operative management be applied. To that end we would like to recommend that the surgical community continue to refer to high-explosive fragments as 'shrapnel,' and,

if in future military conflicts steel balls are encased in exploding casings, that we refer to them as 'grape shot and canister.'

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TIMOTHY C. FABIAN, M.D.
Memphis, Tennessee

September 12, 1989

Dear Editor:

We commend the leadership in pediatric trauma care provided by Eichelberger and his colleagues from the Children's Hospital National Medical Center in Washington, but were somewhat disconcerted by the conclusions in their recent paper 'Abdominal CT in Children with Neurological Impairment Following Blunt Trauma—Abdominal CT in Comatose Children' (*Ann Surg* 1989; 210:229-233). In their prospective study examining indications for abdominal CT in 482 consecutive children, they observed that 28% of their study group with a Glasgow Coma Scale (GCS) less than 8 had significant intra-abdominal injury compared to 8% of those with a GCS more than 8. This finding correlates with similar previous analyses,^{1,2} and the authors conclude appropriately that children with severe neurologic impairment are at higher risk for intra-abdominal injury—an important message. They then review the cases of 11 children who had a GCS less than 8 as their only indication for abdominal CT scanning, and noted that the scan was normal in each case. Based on this small sample, they surmise that abdominal CT scanning is unjustified in these high-risk children without corroborative signs of abdominal trauma. To support this contention, they catalog the indications for abdominal CT in children with a GCS less than 8 who had significant abdominal injury. Abdominal distension, absent bowel sounds, and abrasions were the most frequent. But surely the authors recognize that these 'indications' are subjective and nonspecific in the setting of multisystem trauma. Furthermore the authors cite the report by Beaver et al.¹ documenting the absence of telltale signs in 22% of their children in this precise scenario. In addition other groups have reported an increasing rate of intestinal perforation in children after blunt trauma, perhaps due to the wider use of seatbelts.^{3,4} Delayed recognition of intra-abdominal trauma has the greatest penalty in the critically injured and may be the precipitating event for inexorable multiple-organ failure. Finally recent studies confirm that unrecognized intraperitoneal hemorrhage remains a common cause of preventable death in children.⁵ Authorities in pediatric trauma have admonished for years that children compensate extremely well for acute blood loss but deteriorate precipitously when this capacity is exceeded.⁶ Thus, in reflecting on the weight of available literature as well as our experience,⁷ we submit that diagnostic pursuit of occult abdom-

inal injury is mandatory in the multisystem-injured child with neurologic impairment.

The more common issue of debate is the relative merit of abdominal CT scanning *versus* diagnostic peritoneal lavage. Abdominal CT scanning in the child is not consistently reliable to exclude intestinal perforation or pancreatic fracture.⁸ Other reports⁹ and our experience⁷ continue to demonstrate the extreme sensitivity of DPL in the pediatric age group. We have found the closed-wire technique of peritoneal access particularly valuable in the child, and have been impressed with its simplicity, safety, and sensitivity. Thus we would concur that abdominal CT scanning is not mandatory in the high-risk child but recommend diagnostic peritoneal lavage as a safer and more cost-effective alternative. In fact Eichelberger and his colleagues^{10,11} previously championed DPL as an integral component of the initial evaluation of the critically injured child and have generally embraced an aggressive operative approach.¹² We wonder if they have changed their philosophy or if we have misinterpreted their timely manuscript.

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RENATO POGGETTI, M.D.
ERNEST E. MOORE, M.D.
FREDERICK A. MOORE, M.D.
CHARLES M. ABERNATHY, M.D.
Denver, Colorado

November 2, 1989

Dear Editor:

We thank Dr. Poggetti and colleagues for their interest in our paper on abdominal computed tomography (CT) in neurologically impaired children,¹ and we welcome the opportunity to respond to their concerns. We undertook this study to evaluate the role of neurologic impairment as an indication for CT ex-

amination, and to test the hypothesis that children with severe neurologic impairment are at increased risk for intra-abdominal injury than children with little or no neurologic impairment. As a point of clarification, we did not conclude that CT scans were 'unjustified' in children with isolated neurologic impairment, but merely that neurologic impairment, in the absence of physical signs of abdominal injury, was 'a low-yield indicator of underlying abdominal injury.' We leave the problem of justifying the use of resources to the individual physician.

We believe one of the most important findings of our study is that all of the children with both neurologic impairment and abdominal injury (n = 25) presented with two or more physical signs of abdominal injury. Furthermore most of these indicators (hematuria, abrasion, blood per nasogastric tube, and distension) are not 'subjective and nonspecific,' but rather represent objective measures that are reliably recognized. We think that our use of a 'check list' of abdominal signs by physicians requesting CT exams resulted in more accurate documentation of abdominal signs than did previous studies,^{2,3,4} and underscores the importance of careful physical examination of the injured child.

Dr. Poggetti is correct to point out that our study is limited by the small number of neurologically impaired children who had neither abdominal signs nor injury. However these children are from a series of 482 consecutive abdominal CT scans representing more than 4 years of experience. The provision of 'denominator data' represents a significant improvement over previous studies^{3,4} that give no numerical context for the series they report.

Dr. Poggetti and colleagues raise the possibility of missing intestinal perforation after blunt trauma. Recently we reported our experience with bowel injuries occurring in 547 consecutive children with blunt abdominal trauma.⁵ We detected all six cases of perforated viscus with CT by demonstrating small amounts of free intraperitoneal air (n = 4), and bowel thickening or unexplained peritoneal fluid (n = 2). All children had significant findings on physical examination.

The diagnostic utility of CT scans *versus* peritoneal lavage is a controversial topic, as Dr. Poggetti accurately notes. We did not perform routine peritoneal lavage on this series of patients; therefore we believe that our data may not be used correctly for comparative purposes. We agree that diagnostic peritoneal lavage is appropriate for children at high risk of intestinal perforation or rupture, as in the child with 'lap belt complex' injury.⁶ Physical examination continues to be an important component of the evaluation of children after blunt trauma. Reliance on radiographic investigation without attention to physical signs will hinder progress in improving care of injured children.

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GEORGE A. TAYLOR, M.D.
MARTIN R. EICHELBERGER, M.D.
Washington, D.C.

October 15, 1989

Dear Editor:

The article 'Ileal Pouch–Anal Anastomosis: Comparison of Results in Familial Adenomatous Polyposis and Chronic Ulcerative Colitis' by Dozois and colleagues (*Ann Surg* 1989; 210: 268–273) is highly significant in its presentation and the discussion it evoked. The article reports that pouchitis occurred in 22% of ulcerative colitis patients and in 7% of polyposis patients. In the discussion Professor J. Albertus Myburgh observed remarkable colonic metaplasia or 'colonization' of the mucous membrane of the pouch, adenomatous polyps in the pouch, and terminal ileum proximal to the pouch, hence with recurrence of the basic disease in ulcerative colitis and polyposis.

Could this be ascribed to loss of the ileocecal sphincter, which occurs with loss of the gastric pyloric sphincter with intestinalization of the gastric mucosa? 'Gastricization' of the esophageal mucosa occurs with loss of an effective esophagogastric sphincter with change from squamous to columnar epithelium.

Dr. Lester Martin reports the 44% incidence of night-time soiling in the presented series. In his own series he has reduced the incidence to less than 3%, which he ascribes to retention of the transitional epithelium overlying the columns of Morgani above the pectinate line, thereby maintaining an intact autonomic reflex arc. This transitional epithelium could be joined with the transitional epithelium at the apex of the ileal protuberance, thereby preserving the ileocecal muscular junction.^{1,2}

In doing ileoproctostomies, I have retained the ileocecal 'sphincter' and 5 mm of the adjacent cecal wall. These procedures were for familial polyposis, multiple colonic polyposis, and massive acute colon bleeding. The patients appeared to do better than patients without retention of the terminal ileum with the ileocecal sphincter. This was presented at the surgical section of the California Medical Association convention in 1966.

Other potential advantages in retention of the ileocecal sphincter, besides possible effect on 'colonization,' is continence and possible production of the phenomena described by Pemberton in use of his mechanical device to control ileostomy effluent.³ With the build-up of back pressure, the ileum tends to dilate and form its own pouch.

Dr. R. Emblem and associates reported a 5-year follow-up on 32 patient, in whom a mucosal dissection was performed from above with preservation of the distal 1 to 2 cm of the mucosal brim distal to the EEA stapled anastomosis. They did not do a diverting ileostomy, although they now recommend that a loop ileostomy be part of the surgical strategy.

Results were satisfactory in terms of postoperative complications, continence, and stool frequency. Distal ileal capacity and distensibility were significantly better. These were compared with a group of 26 patients done from the perineal approach. They concluded that the results after radical mucosectomy by the perineal approach were not acceptable. The most important factor in conserving continence seems to be avoidance of anal dilatation.⁴

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LAWRENCE BRASLOW, M.D.
Riverside, California

December 29, 1989

Dear Editor:

Doctor Braslow raises several interesting and controversial issues regarding the ileal pouch–anal anastomosis (IPAA).

The exact cause of pouchitis is unknown, although it appears, in some way, to be related to bacterial overgrowth and colonic metaplasia, which create an environment favoring the development of ulcerative colitislike conditions.¹ The clinical syndrome of pouchitis is reported to occur in 7% to 42% of colitis patients and rarely, if ever, in polyposis patients.¹ The syndrome appears to be more prevalent in those colitis patients with preoperative extraintestinal manifestations and may be associated with a recrudescence of the same manifestations, raising the possibility of a common etiology (Lohmuller, Pemberton, and Dozois, unpublished data). However adenomatous polyps in ileal pouches rarely have been seen in polyposis patients^{1,2} and may, in fact, be a manifestation of the underlying disease because ileal polyps can sometimes be found in polyposis patients before colectomy and even proximal to a Brooke ileostomy.³ It is doubtful that pouchitis is directly attributable to the loss of the ileocolonic valve, and leaving it in place may interfere with neorectal emptying and leave residual disease.

The incidence of incontinence after IPAA reported by various authors varies considerably depending on the definition of incontinence, the gender and age of the patients, and the nature of the underlying disease. In the current report, the problem of nighttime 'spotting' (staining of undergarments twice a week or less often) was observed in 40% of the colitis patients and in 26% of the polyposis patients. A previous report from our institution has shown that, in colitis patients at least, both nighttime spotting and gross incontinence were noted to diminish considerably with time, from 30% at 1 year to 13% at 3 years.⁴ Whether this degree of imperfect continence can be overcome by leaving intact the transitional epithelial zone is debatable. From the standpoint of continence, the only controlled study conducted thus far has failed to demonstrate a definite advantage of this technique.⁵ We have found recently that fingerlike projections of rectal mucosa extend within 1 cm of the dentate line in 89% of colitis patients (Ambroze, Pemberton, and Dozois, unpublished data), indicating that leaving the transition zone in place does not eliminate the disease and its inherent risks, including adenocarcinoma. Indeed, among 16 colitis patients in whom this technique was used, histopathologic evidence of residual disease was seen in 14 patients, including moderate dysplasia in four patients and unsuspected carcinoma in one patient.⁶ With regard to polyposis patients, Emblem and colleagues⁷ have found that 10 of 13 patients with a straight ileoanal anastomosis without a surgically created reservoir in whom this mucosal area was retained developed further polyposis in the im-

mediate vicinity of the anastomosis. Finally, when we applied the same stringent definition of continence to polyposis patients, the incidence of night-time spotting after ileorectostomy, where the entire rectal mucosa was retained, did not differ very much from that seen after IPAA (Ambroze, Dozois, and Pemberton, unpublished data). Similarly Newton and Baker⁸ have reported some degree of incontinence after ileorectostomy in 22% of their polyposis patients. One would not anticipate such results if anal dilatation and/or removal of the transition zone were solely responsible for night-time incontinence.

We must continue to look for ways to improve the functional results of IPAA, but ideally this should be accomplished without compromising our opportunity to cure the offending colorectal disease.

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ROGER R. DOZOIS, M.D.
Rochester, Minnesota

December 27, 1989

Dear Editor:

In an attempt to formulate treatment guidelines for early postoperative small bowel obstruction, Pickleman and Lee¹ do not advocate the routine performance of upper GI x-rays. This may be so for the contrast radiographic method they use, *i.e.*, the barium follow-through examination. No mention is made, however, of the diagnostically more useful enteroclysis (small bowel enema) method. I wish to bring to the attention of the authors a recent publication from the departments of Radiology and Surgery in Oxford, emphasising specifically the contribution of enteroclysis to the diagnosis of early postoperative intestinal obstruction.²

Enteroclysis is an easy examination to perform and gives consistently good results.³ The main advantage of enteroclysis is the demonstration of all small bowel loops in a state of luminal distention.⁴ The most consistent sign of obstruction on enteroclysis is a constant segment of narrowing, with an acute transition in caliber between the distended proximal loops and the collapsed distal intestine. Adhesive obstruction can be shown with a high degree of reliability and an overall prospective accuracy of about 90%.⁵

It is much faster to perform enteroclysis than the barium follow-through examination, and enteroclysis avoids the logistical difficulties involved in performing intermittent protracted serial radiography on an ill patient. However, in some patients with marked obstruction, it may be necessary to take delayed radiographs because of the slow transit of barium in the dilated fluid-filled loops. In these patients concentrated barium may be used and the enteroclysis tube may be left *in situ* after the examination to aid intestinal decompression.

Small bowel obstruction in the early postoperative period demands a rapid and accurate diagnostic method. Unfortunately enteroclysis continues to receive little attention in the surgical literature. The high reliability of a positive or negative result of enteroclysis emphasises its importance in the evaluation of obstruction. In difficult cases during the early postoperative period, knowledge of the level, degree and probable cause of obstruction, as shown by enteroclysis, allows confident conservative management or early reoperation.

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TARIK F. MASSOUD, M.B.
Oxford, England

January 15, 1990

Dear Editor:

Dr. Massoud brings to our attention the underused method of small bowel enteroclysis, which, he rightly notes, has received scant attention in the surgical literature dealing with small bowel obstruction. I suspect that this is not an example of surgical Neanderthal logic but rather that we surgeons have come to grips with the inconsistencies of the clinical signs and the laboratory tests in patients with small bowel obstruction, and have learned the hard way that early operation is the safest course of action in many patients.

What I wished to stress in my article was that early postoperative bowel obstruction may represent an entity distinct from the usual adhesive small bowel obstruction occurring remotely after celiotomy.

In our series none of the 101 patients had ischemic bowel, and I would therefore disagree with the emphasis placed on Dr. Massoud's statement that 'Small bowel obstruction in the early postoperative period demands a rapid and accurate diagnostic method.' Patients who become distended and vomit after operation will have either ileus or small bowel obstruction. In my opinion the treatment is similar, mainly nasogastric suction for a sufficient period of time to allow resolution of either process, with reoperation reserved for those patients who do not improve in 10 or 14 days or for the rare patient who manifests evidence of ischemic bowel.

JACK PICKLEMAN, M.D.
Maywood, Illinois

December 20, 1989

Dear Editor:

Berkowitz and colleagues (Ann Surg 1989; 210:782-786) have properly emphasized the critical importance of maintaining an aggressive policy of graft surveillance to identify correctable lesions before graft occlusion. However, I must criticize the methodology used in their calculations of cumulative patency, in which graft lesions treated successfully by percutaneous transluminal angioplasty before graft occlusion are retained as continuously patent in the primary patency category. At the very least, assisted primary patency should have been used because they allude to this point. The issue of contention here deals with the fact that a similar lesion with a still-functioning graft treated by a direct operative approach such as patch angioplasty would be considered (and properly so) as an end-point failure for primary patency and then be placed into a secondary patency category. Clearly the choice of therapies should not be the determinant for categorizing the placement of a 'failing' graft, so long as some form of therapy is instituted. Even more difficult is how to categorize such lesions to which therapy is not applied; presumably these lesions would progress in their natural history to occlusion and obvious failure. These distinctions are important in that the predictive value of procedures, as determined by cumulative function curves, can be enhanced.

HERBERT DARDIK, M.D.
Englewood, New Jersey

February 1, 1989

Dear Editor:

Dr. Dardik did not read carefully the Methods section of our paper, in which we clearly stated that 'Primary patencies were also calculated, in which any occlusion or reintervention, no matter how minor, was considered an end point for graft patency.' By reintervention, we included percutaneous transluminal

angioplasty (PTA) or minor surgical procedures, such as vein patch angioplasty and short extension grafts around proximal or distal stenoses. We made no distinction between PTA and surgery and both are end-points for primary patency.

Furthermore we clearly stated our definition of cumulative patency, as opposed to primary patency: 'Cumulative patency reported here includes grafts, in which patency was maintained by treating stenotic lesions before graft occlusion. It has been suggested that this be referred to as 'assisted' primary patency to differentiate it from secondary patency, which includes re-opened, occluded grafts.' In this definition, we again make no distinction between treating a stenotic lesion by PTA or surgery. We agree with Dr. Dardik that the choice of therapy for treating a 'failing' (stenotic) graft should not be the determinant for categorizing its patency and we have not done so.

We recognize that the initial recommendations of the Committee on Reporting Standards for Vascular Surgery recommended using the term 'secondary' patency for all graft interventions, regardless of whether the graft was stenotic or occluded.¹ This generated some controversy and, in a Letter to the Editor and a response by Rutherford,² the term 'assisted' primary patency was suggested as the proper term for reporting patency of treated stenotic grafts to clearly differentiate it from primary patency (no intervention) and secondary patency (intervention in stenotic or occluded grafts). We believe that these are valid distinctions and have used 'assisted' primary patency in our article.

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HENRY D. BERKOWITZ, M.D.
Philadelphia, Pennsylvania

Current Management of Malignant Melanoma

The incidence of cutaneous melanoma is increasing worldwide; this annual rate of increase, 4%, is higher than for any other malignancy, except lung cancer in women. It has been estimated that by the year 2000, 1 in every 90 persons will develop melanoma. The cause of this rising incidence is unknown but may be related to increasing ultraviolet exposure due to loss of the earth's protective ozone layers. Because the cure rate for thin melanomas, those that measure 0.75 mm in thickness or less, is more than 95%, we need national programs to focus public awareness on changing pigmented lesions. Public campaigns in Australia and Scotland have demonstrated the effectiveness of such programs in establishing early diagnosis, when surgical treatment is most effective.

There are two important questions regarding the current surgical management of primary cutaneous melanoma.

1. How widely should the primary lesions be excised?
2. How should regional lymph nodes be managed?

Two papers in this issue of *Annals of Surgery* have implications for both questions. In an important paper on late melanoma recurrences, Crowley and Siegler review 168 patients with late (10 or more years) recurrences; this information was collected from the large melanoma database at Duke University. Of a total of 651 patients who had been followed for 10 or more years, 168 (approximately 25%) developed late recurrences. This is the highest incidence of late recurrences yet reported and emphasizes the importance of long-term follow-up. They observed recurrences of ocular melanoma 45 and 47 years after treatment of the primary lesion. Recurrences of cutaneous melanoma have been delayed as long as 40 years, particularly in women whose primary lesion was on the extremity. Of particular importance for primary surgical treatment is the observation that 70% of the delayed recurrences after 10 years occurred in the local skin surrounding the primary site or in the regional lymph nodes. This indicates that cutaneous melanoma may remain clinically dormant for long periods of time. It also underscores the importance of long-term follow-up in evaluating newer, more conservative surgical approaches.

The extent of surgical resection of skin and subcutaneous tissues surrounding the primary melanoma remains controversial. No one has shown how close the surgeon can come to a primary melanoma without increasing the incidence of local recurrence. Since W. Sampson Handley, in 1907, recommended a 5-cm radial margin around the primary lesion, such a margin has been the treatment of choice until very recently. A number of investigators have reported that thin lesions (measuring less than 0.76 mm) rarely recur with margins of 1 to 2 cm. A recently reported World Health Organization (WHO) melanoma group trial randomized lesions up to 2 mm in thickness to narrow excisions of 1 cm *versus* a 4-cm radial margin. There was no statistically significant difference in the local recurrence rate in this randomized trial, but all the observed local recurrences were in the narrow-margin group. Follow-up in this series was short, and such a trial must have a longer follow-up to be accepted as valid.

Until the optimum width of excision of a primary melanoma can be determined by longer follow-up of current trials, we have adopted the following guidelines based on the observation that the risk of local recurrence is directly proportional to the depth of the primary melanoma:

1. Clark's level II melanoma, or thin Level III lesions that measure less than 0.75 mm in thickness: Excision with 2 to 3 cm radial margins.
2. Clark's level III melanoma, lesions that are thicker than 0.75 mm, and all Clark's Level IV melanomas: Excision with 3 to 4 cm radial margins.
3. Clark's level V melanoma and all melanomas thicker than 4 mm: Wide excision with 5-cm radial margins around the primary site, which includes the underlying fascia, because these lesions are more likely to have microsatellites surrounding the primary lesion and involvement of the subdermal lymphatics close to the primary lesion.

Except on the face, from a practical standpoint, there is little difference between narrow and wide excisions in regard to the cosmetic result, as long as the defect can be closed primarily by rotation and advancement flap techniques.

Surgical Management of the Regional Lymph Nodes

There is general agreement that regional lymphadenectomy is indicated for the patient who has suspicious or pathologically proved metastases to the regional lymph nodes. Contrary to the pessimism in the early literature, as shown in this issue's paper by Bevilacqua, Coit, and associates from Memorial Sloan-Kettering Cancer Center, 32% of these patients with axillary metastases will survive 10 years. Furthermore patients with only one clinically positive lymph node had a 50% chance of long-term survival.

At initial examination, 90% of melanoma patients have no clinical evidence of metastases to the regional lymph nodes or distant sites. Such clinical stage I (CSI) patients present a common therapeutic dilemma regarding the management of the regional nodes. Some surgeons advise immediate elective lymph node dissection (ELND) for these patients; others adopt a program of 'watch and wait,' with careful follow-up examinations and delayed therapeutic lymphadenectomy if metastases develop in the regional nodes. The benefit of elective or prophylactic lymph node dissection for patients who are CSI is controversial. Several long-term, retrospective, biostatistical studies from single institutions have demonstrated a small but significant therapeutic benefit from ELND for patients with CSI melanomas of an intermediate Clark's level or Breslow thickness. Furthermore the survival rates after lymph node dissection are 15% to 25% higher for patients with clinically occult metastases than for patients who have clinically detectable disease. As noted by the Memorial Sloan-Kettering group, there was a statistically significant improved survival rate at 5 years in patients with occult metastatic disease. This improved survival rate presumably was due to resection of metastatic disease at an early point in its natural history while it is still confined to the lymphatic basin.

Despite this apparent benefit of ELND, randomized clinical trials have not demonstrated a statistically significant overall survival advantage from ELND when the entire group of patients with CSI cutaneous melanoma undergo ELND. However data from the randomized WHO trial indicate that patients with intermediate level melanoma of the extremities who underwent ELND had survival rates that were approximately 11% higher than did patients who underwent delayed therapeutic lymphadenectomy. This difference was not statistically significant because there were small numbers of patients in this subset of the trial.

Two large randomized trials are in progress for melanomas of intermediate depth, 1.5 to 3.99 mm in thickness, by the American Cooperative Groups and the WHO Melanoma Group. However the results of these trials will not be available for many years and will require long-term follow-up, as emphasized by Crowley and Siegler in their paper in this issue. Until these data are available, each surgeon must make an individual decision for each patient when recommending ELND. However the difficulty, in our mobile society, of maintaining close follow-up of these patients at 3-month intervals for periods of 10 years or more must be recognized. It has been our policy to recommend regional lymphadenectomy for all those patients who are of young or middle age and who have lesions measuring more than 1.5 mm in thickness. In our center the incidence of clinically occult nodal metastases in this group of patients is 36%. Because the incidence of occult metastases will be low (about 10%) for lesions thinner than 1.5 mm, the use of ELND in this group is highly individualized, and no general guidelines can be proposed.

We are investigating an alternative approach to this problem of accurately staging patients with CSI melanoma. New operative techniques have been developed for identifying the lymphatic drainage path from the site of the primary melanoma to the individual sentinel lymph node(s) within the regional lymphatic basin. This permits selective lymphadenectomy of these draining lymph nodes and intraoperative examination by frozen section, resulting in accurate pathologic staging. Thus, with a relatively minor procedure, surgeons can select those patients who have metastatic disease who will benefit from a therapeutic lymph node dissection, and thereby avoid the morbidity of radical lymphadenectomy in the patients who do not have nodal metastases.

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Axillary Dissection in Melanoma

Prognostic Variables in Node-positive Patients

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We evaluated the importance of 14 clinical and pathologic variables as determinants of prognosis in patients with malignant melanoma and positive regional lymph nodes at axillary dissection. The records of 197 patients operated on between 1974 and 1984 were reviewed. Univariate analysis indicated as prognostically significant the number ($p < 0.001$) and percentage ($p < 0.001$) of positive nodes, highest nodal status ($p < 0.001$), macroscopic or microscopic nodal metastases ($p = 0.002$), presence or absence of extranodal disease ($p = 0.003$), clinical stage (III *versus* less than III, $p = 0.015$), and site (considered as trunk *versus* other locations, $p = 0.02$). However, by multivariate analysis, only three variables were shown to be independent determinants of survival: percentage of positive nodes ($p = 0.004$), presence or absence of extranodal disease ($p = 0.012$), and site (trunk *versus* other locations, $p = 0.019$). Combining these three variables, subsets of patients with markedly different prognoses could be generated. It is possible to predict a favorable outcome for patients with less than 10% positive nodes, no extranodal disease, and a primary lesion at a site other than the trunk. It is also possible to recognize that the prognosis is very poor for patients with extranodal disease and truncal primary lesions, regardless of the percentage of positive lymph nodes. Finally it was verified that the prognosis is always unfavorable when the percentage of positive lymph nodes is very high.

A PRIMARY DETERMINANT of prognosis in malignant melanoma is the presence or absence of pathologically involved lymph nodes. Detailed analyses of lymph node status has demonstrated the significance of absolute number¹⁻⁸ and percentage^{2,3} of positive nodes, macroscopic *versus* microscopic nodal involvement,^{2,9} and extranodal melanoma at node dissection.⁷ In ilioinguinal dissection the significance of distal

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(superficial) and proximal (deep) positive nodes also was assessed.¹⁰⁻¹³

The prognostic influence of lymph node-related variables previously has not been examined exclusively for patients undergoing axillary lymph node dissection (ALND). In this study a group of patients with proved melanoma metastatic to axillary nodes following ALND was analyzed.

The main objective was to determine whether further prognostic information can be obtained in the patient with malignant melanoma undergoing ALND if we append to the clinical preoperative data the pathologist's evaluation of the surgical specimen.

Patients and Methods

The medical records of 197 patients with melanoma metastatic to axillary nodes undergoing ALND at Memorial Sloan-Kettering Cancer Center between 1974 and 1984 were reviewed.

Stage was defined according to the American Joint Committee on Cancer (AJCC) system proposed in 1983 (Table 1).¹⁴ All patients classified as pathologic stage III were included. Ten cases in which the largest lymph node ranged from 6 to 9 cm were included in the study group. This allowed a full evaluation of the importance of lymph node size. Excluded from the analysis were patients with metastases to two nodal groups, and patients with intransit or distant metastases.

The prognostic importance of the following non-lymph node-related variables was evaluated: patient sex, age, primary site, level, thickness, ulceration, and clinical stage. The primary site was designated as upper extremity, trunk,

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TABLE 1. *Melanoma Staging System (American Joint Committee on Cancer, 1983)*

Primary Tumor	
TX Unknown, cannot be assessed	
T0 Atypical melanocytic hyperplasia, <i>in situ</i> , Clark I	
T1 Clark II, ≤ 0.75 mm	
T2 Clark II, 0.76–1.50 mm	
T3 Clark IV, 1.51–4.0 mm	
T4 Clark V, >4.0 mm or satellites within 2 cm of primary tumor	
Lymph Nodes	
NX Unknown, cannot be assessed	
N0 Negative	
N1 One regional node station, nodes mobile, ≤ 5 cm diameter or negative nodes and <5 intransit metastases	
N2 More than one node station positive, nodes >5 cm or fixed, >5 intransit metastases, or any intransit metastases with positive nodes	
Distant Metastases	
MX Unknown, cannot be assessed	
M0 None	
M1 Skin or subcutaneous tissue beyond the primary nodal area	
M2 Visceral	
Stage Grouping	
Stage IA	T1, N0, M0
Stage IB	T2, N0, M0
Stage IIA	T3, N0, M0
Stage IIB	T4, N0, M0
Stage III	Any T, N1, M0
Stage IV	Any T, N2, M0, or Any T, any N, M1–2

Table modified from Coit and Brennan.¹³

or unknown (when patient and physician were unable to determine its site). Extremity lesions were further divided into proximal and distal to the elbow. Trunk lesions were classified as midline when they were located within 3 cm of the midline and were otherwise considered lateral. Clark level and Breslow thickness of all lesions not removed at Memorial Sloan-Kettering Cancer Center were reviewed by a pathologist of this hospital before ALND. We used a broad definition of ulceration that included all patients describing bleeding of the lesion with minor trauma as well as those with ulceration reported on histologic review.

The lymph node-related variables analyzed included the number of positive lymph nodes, the percentage of positive nodes (number of positive/total number removed $\times 100$), the size of the largest positive lymph node (in millimeters), the highest nodal status, the level of the highest positive node, the invasion of soft tissue from diseased nodes (extranodal disease), and the gross nodal appearance (macroscopic *versus* microscopic metastases).

The highest nodal status was described as positive when the highest dissected lymph node was affected by metastatic melanoma.

The level of the highest positive node was referred to as I when lateral, II when behind, and III when medial to the pectoralis minor muscle.

The gross nodal appearance was defined as macroscopic when either the operating surgeon or the prospecting pa-

thologist described the presence of visible or palpable disease in the surgical specimen that was subsequently confirmed histologically. If neither the surgeon nor the pathologist described visible or palpable disease in the surgical specimen and histologic review subsequently revealed metastatic melanoma, the nodal involvement was classified as microscopic.

The surgical technique followed well-established routines for ALND and included removal of the entire axillary contents, with the pectoralis minor muscle, up to and including the level III lymph nodes medial to it, exposing the costoclavicular ligament.

The purpose of the operation was therapeutic in 150 patients classified as clinical stage III, while the intent was prophylactic in 47 patients who were clinically understaged as IB, IIA, or IIB (Table 2).

The main objective of the statistical analysis was to assess the dependence of the rate of death from melanoma on the explanatory variables. Time was measured from the date of ALND to the date of death or last follow-up. Survival was estimated for each variable by the product-limit method of Kaplan and Meier.¹⁵ Log rank test¹⁶ was used to check for dependence of survival on each variable taken one at a time.

Proportional hazards regression¹⁷ was used to incorporate all the explanatory variables in the same model. Forward stepwise procedure and likelihood ratio tests were used to select the variables with the greatest prognostic value. Interaction effects among the variables were also considered. The adequacy of the proportional hazard model to the data was checked by fitting separate proportional hazard models to partitions of the data determined by a given categorical variable. The coefficients estimated for each partition should not differ substantially unless there was an interaction effect. Cumulative hazard plots were also generated to visually check the assumption of the proportionality of the hazard rates.

Whereas in the univariate analysis age, primary lesion thickness, number of positive nodes, percentage of positive nodes, and size of the largest node were used to generate subsets of categorical variables, in the proportional hazards regression they were treated as continuous variables.

Pairwise associations between variables were evaluated by a *t* test for linear correlation (two continuous variables), one-way analysis of variance (categorical versus continuous variables), or a contingency table analysis using a chi square or an exact test (two categorical variables).¹⁸

To display the relationship of a continuous variable and survival time, a predictive plot was generated. The predicted median survival for a given set of covariates *x* is the time *t* such that

$$\hat{S}(t) = (0.5)^{\exp(\mathbf{x}'\hat{\beta})}$$

where $\hat{\beta}$ is the proportional hazards regression coefficient,

TABLE 2. Univariate Analysis of Variables not Related to Pathologic Status of Lymph Nodes

Variable	Number of Patients	Five-year Survival $\pm$ SE (%)	Ten-year Survival $\pm$ SE (%)	Cox-Mantel (p)
Sex				
Male	138	37.4 $\pm$ 4.4	30.7 $\pm$ 4.9	NS
Female	59	38.0 $\pm$ 6.7	38.0 $\pm$ 6.7	
Age (years)				
<35	42	51.5 $\pm$ 7.9	51.5 $\pm$ 7.9	NS
35-50	68	31.9 $\pm$ 6.0	29.3 $\pm$ 6.1	
50-65	61	42.1 $\pm$ 6.9	28.0 $\pm$ 8.6	
>65	26	21.8 $\pm$ 8.5	21.8 $\pm$ 8.5	
Site				
Arm—distal	15	46.7 $\pm$ 12.9	46.7 $\pm$ 12.9	NS
Arm—proximal	26	64.0 $\pm$ 9.7	53.3 $\pm$ 12.6	
Trunk—lateral	117	28.9 $\pm$ 4.5	23.8 $\pm$ 5.1	
Trunk—midline	14	49.0 $\pm$ 13.6	39.2 $\pm$ 14.0	
Unknown	25	41.1 $\pm$ 10.1	41.1 $\pm$ 10.1	
Site				
Trunk	131	31.2 $\pm$ 4.3	25.7 $\pm$ 4.7	0.02
Nontrunk	66	51.1 $\pm$ 6.4	47.9 $\pm$ 6.8	
Clark's Level				
II	15	60.0 $\pm$ 12.6	60.0 $\pm$ 12.6	NS
III	45	29.0 $\pm$ 7.7	23.2 $\pm$ 8.0	
IV	72	42.9 $\pm$ 6.0	34.3 $\pm$ 6.8	
V	11	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0*	
Undetermined	54			
Breslow's Thickness (mm)				
≤ 0.75	8	50.0 $\pm$ 17.7	50.0 $\pm$ 17.7†	NS
>0.75-1.5	19	40.9 $\pm$ 12.7	20.5 $\pm$ 15.8	
>1.5-4.0	50	38.8 $\pm$ 7.3	29.1 $\pm$ 8.1	
>4.0	20	28.1 $\pm$ 11.8	28.1 $\pm$ 11.8‡	
Undetermined	100			
Ulceration				
Absent	105	37.4 $\pm$ 5.1	31.0 $\pm$ 5.4	NS
Present	57	40.8 $\pm$ 6.8	37.4 $\pm$ 7.0	
Undetermined	35			
Clinical Stage				
1B	5	66.7 $\pm$ 27.2	33.3 $\pm$ 27.2	NS
2A	30	46.9 $\pm$ 9.6	31.3 $\pm$ 14.3	
2B	12	50.0 $\pm$ 16.4	37.5 $\pm$ 16.4	
3	150	33.9 $\pm$ 4.1	32.8 $\pm$ 4.1	
Clinical Stage				
<III	47	49.5 $\pm$ 8.1	32.6 $\pm$ 10.1	0.015
III	150	33.9 $\pm$ 4.1	32.8 $\pm$ 4.1	

NS, not significant.

* Survival at 54 months (last follow-up in this category).

† Survival at 117 months (last follow-up in this category).

‡ Survival at 89 months (last follow-up in this category).

and $\hat{S}(t)$ is the smoothed estimate of the underlying survival function as derived by Link.¹⁹ Details of this procedure are discussed by Heller and Simonoff.²⁰

The statistical analysis was performed using the BMDP statistical package (BMDP Statistical Software, Los Angeles, CA).²¹ The critical significance level of 5% was chosen.

Results

The study group comprised 138 male (70%) and 59 female (30%) subjects. The median age was 48 years (range, 8 to 83 years).

One hundred twenty patients died of melanoma (60.9%), 2 to 105 months after ALND (median, 17

months). The five- and ten-year survival rates ($\pm$ standard error) for the entire group were 37.7% (± 3.7) and 32.7% (± 4.1), respectively. The remaining 77 patients (39.1%) had a follow-up ranging from 4 to 164 months (median, 62 months). Of these, by the time of closure of the study, 67 had no evidence of melanoma, 4 were alive with disease, and 6 had died of other causes. The univariate analysis revealed that sex, age, site, Clark's level, Breslow's thickness, ulceration, and clinical stage did not affect prognosis when considered in this group of pathologically node-positive patients (Table 2). However, when site was considered as trunk *versus* other or unknown locations, the difference in survival rate became statistically significant (Table 2) and for this reason this variable was included in the multivariate analysis.

The following lymph node-related variables were prognostically important by univariate analysis: number and percentage of positive lymph nodes, highest nodal status, presence or absence of extranodal disease, and microscopic or macroscopic nodal appearance (Table 3). Conversely the size of the largest positive node ($p = 0.87$) and the level of the highest positive node ($p = 0.78$) were of no prognostic value.

In the multivariate analysis, only variables that were significant in the univariate approach were considered. From the 197 patients, only 147 had complete information on all these variables and these made up the multivariate sample. Three variables were selected into the final proportional hazards regression: percentage of positive lymph nodes, extranodal disease, and site of the primary lesion. No other lymph node-related variable showed independent prognostic importance in the proportional hazard regression. The hypothesis that all the regression coefficients were zero was rejected ($p < 0.001$). Table 4

shows the summary of the multivariate analysis in terms of likelihood ratio tests, coefficients, and standard errors of the selected variables.

Table 5 shows the associations between lymph node-related variables. Percentage of positive nodes and extranodal disease, variables that were selected in the multivariate model, are uncorrelated. The other variables, which were not selected in, are highly correlated, mainly with percentage.

As most previous investigators have considered the absolute number rather than percentage of positive nodes, the association of absolute number, percentage, and total number of recovered nodes was further analyzed. The correlation between percentage and number of positive nodes was high ($r = 0.85$, $p < 0.001$). Percentage of positive nodes did not correlate with the total number of recovered nodes ($r = 0.05$, $p = 0.13$). Using the same cutoff points defined in the univariate analysis, Table 6 shows that a low positive lymph node percentage (10%

TABLE 3. Univariate Analysis of Lymph Node-related Variables

Variable	Number of Patients	Five-year Survival $\pm$ SE (%)	Ten-year Survival $\pm$ SE (%)	Cox-Mantel (p)
Number of positive lymph nodes				
1	102	49.9 $\pm$ 5.5	42.6 $\pm$ 6.1	<0.001
2-3	43	36.9 $\pm$ 7.4	36.9 $\pm$ 7.4	
>3	31	17.4 $\pm$ 7.2	8.7 $\pm$ 7.1	
Undetermined	21			
Percentage of Positive Lymph Nodes				
<10	92	48.1 $\pm$ 6.0	39.9 $\pm$ 6.5	<0.001
10-20	31	26.9 $\pm$ 8.3	26.9 $\pm$ 8.3	
>20	31	18.4 $\pm$ 7.1	9.2 $\pm$ 7.4*	
Undetermined	43			
Status of the Highest Dissected Lymph Node				
Negative	163	42.4 $\pm$ 4.1	36.5 $\pm$ 4.6	<0.001
Positive	27	14.8 $\pm$ 6.8	15.8 $\pm$ 6.8	
Undetermined	7			
Nodal Appearance				
Microscopic	41	58.5 $\pm$ 8.5	47.2 $\pm$ 9.9	0.002
Macroscopic	149	32.8 $\pm$ 4.0	29.4 $\pm$ 4.4	
Undetermined	7			
Extranodal Disease				
Absent	163	41.7 $\pm$ 4.1	36.1 $\pm$ 4.9	0.003
Present	27	17.8 $\pm$ 7.5	17.8 $\pm$ 7.5	
Undetermined	7			
Size of the Largest Lymph Node (mm)				
<20	66	37.6 $\pm$ 6.5	37.6 $\pm$ 6.5	NS
20-40	48	41.8 $\pm$ 7.4	30.3 $\pm$ 9.1	
>40	24	27.8 $\pm$ 9.5	27.8 $\pm$ 9.5	
Undetermined	59			
Level of the Highest Positive Lymph Node				
I	41	31.7 $\pm$ 8.3	26.4 $\pm$ 8.4	NS
II	13	38.5 $\pm$ 13.5	28.8 $\pm$ 13.1	
III	9	22.2 $\pm$ 13.8	22.2 $\pm$ 13.8	
Undetermined	134			

NS, not significant.

* Survival at 107 months (last follow-up).

TABLE 4. Final Proportional Hazard Regression Model. Variables of Prognostic Importance

Variable	Likelihood Ratio Test (p)	Regression Coefficient $\pm$ SE
Percentage of positive nodes	0.004	0.017 $\pm$ 0.005
Extranodal disease	0.012	0.850 $\pm$ 0.307
Site	0.019	0.573 $\pm$ 0.248

or less) in 89.1% of the cases is associated with only one positive lymph node. Conversely 77.4% of patients with more than 20% positive nodes had more than three positive nodes in the axilla.

The number of recovered nodes varied from 10 to 59 for the patients with a positive node percentage of 10% or less, which is similar to the range of 4 to 67 for patients with a positive node percentage greater than 10%. Therefore, in the absence of a correlation between the number of positive nodes and the total number of recovered nodes, the possibility of a pathology bias (of the type 'the more you search the more you find') can be discarded.

In this group of lymph node-positive patients, the survival of clinical stage less than III *versus* clinical stage III patients was significantly different in the univariate analysis (Table 2). However this variable was not included in the multivariate model. This can be explained by the association of clinical stage and percentage of positive nodes. The percentage of positive nodes in the subset of clinical stage less than III was 9.5% ($\pm 6.3\%$) and in clinical stage III it was 16.5% ($\pm 20\%$), a significant difference by t test ($p = 0.03$).

The prognosis in node-positive patients is expressed as the estimated median survival rate in months in Figure

TABLE 5. Associations Between Lymph Node-related Variables

Variables	p
Percentage of positive lymph nodes and	
Number of positive lymph nodes	<0.001*
Size of the largest lymph node	<0.001*
Highest node status	<0.001†
Level of the highest positive node	<0.001‡
Gross nodal appearance	0.010†
Extranodal disease	NS†
Extranodal disease and	
Highest node status	0.015§
Number of positive lymph nodes	NS†
Size of the largest lymph node	NS†
Gross nodal appearance	NS§
Level of the highest positive node	NS

NS, not significant.

* t test for linear correlation.

† t test.

‡ One-way analysis of variance.

§ Chi square.

|| Exact test for $r \times c$ contingency tables.

TABLE 6. Percentage of Positive Nodes Versus Number of Positive Nodes

		Number of Positive Nodes		
		1	2-3	>3
Percentage of Positive Nodes	<10	82	10	0
	10-20	5	20	6
	>20	1	6	24

Both variables transformed to categorical, using the same cutoff points as in the univariate analysis.

1, combining the independently significant variables of percentage of positive lymph nodes, extranodal disease, and primary site. The four distinct curves, situated at progressively lower levels on the Y axis, show how the predicted median survival rate varies as a function of the variables selected into the proportional hazards regression model.

Discussion

Lymph node dissection in malignant melanoma is based on the hypothesis that the disease is locoregional in a proportion of patients with regional lymph node metastases. If the operation is performed at this stage all malignant foci may be eradicated and the patient cured.

Decades of observations have shown the difficulty in achieving this goal. A significant proportion of patients

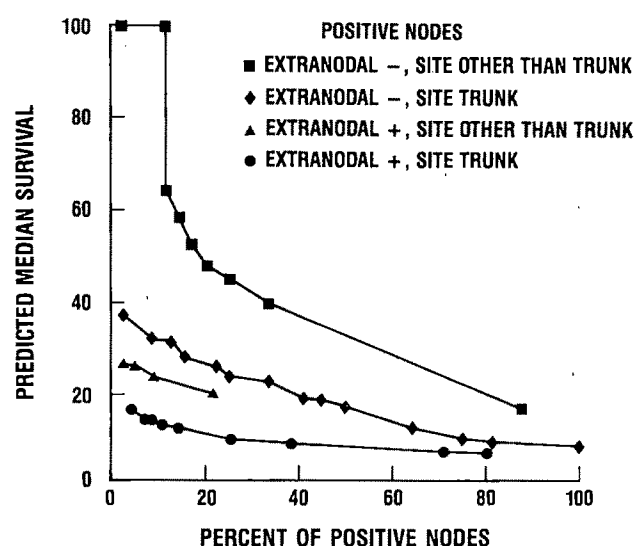
AXILLARY LYMPH NODE DISSECTION IN MELANOMA
PREDICTED MEDIAN SURVIVAL (MONTHS) BY PERCENT
OF POSITIVE LYMPH NODES

FIG. 1. Predicted median survival of patients with the melanoma metastatic to axillary lymph nodes as a function of percentage of positive nodes, presence of extranodal disease, and site of the primary.

with positive nodes will die, even if the lymphadenectomy is performed when the nodes are clinically negative. Conversely some patients with clinically and pathologically positive nodes removed will survive. This demonstrates the importance of defining variables that could help in the definition of true locoregional disease.

Although our primary interest was to evaluate lymph node-related variables, truncal *versus* nontruncal site was ultimately included in our considerations because it was the only non-lymph node-related variable maintaining significance both in the univariate and multivariate analyses. This finding contrasts with the results of other studies in stage III malignant melanoma^{5,22} in which site was not an independent predictor of outcome. As shown in Table 2, site was significant only when subdivided into two groups, trunk and nontrunk. Further subdivision of site into proximal *versus* distal extremity or midline *versus* lateral trunk obscured its significance as an independent predictor of outcome.

Five lymph node-related variables, number and percentage of positive nodes, status of the highest node, macroscopic nodal appearance, and presence of extranodal disease, were statistically significant by the univariate analysis. Only two of these, percentage of positive nodes and presence of extranodal disease, were independent predictors of survival in the multivariate analysis. This disagreement is only apparent because most of the significant univariate variables are associated with percentage of positive nodes (Table 5).

Two lymph node-related variables, level of the highest positive node and size of the largest lymph node, were not significant in predicting survival, even in the univariate analysis.

The level of the highest positive lymph node is a concept borrowed from breast cancer surgery where it was introduced by Berg²³ in 1955 at Memorial Sloan-Kettering Cancer Center. However it is important to note that, even for these tumors, this variable was not universally accepted as an independent predictor of survival. Smith et al.²⁴ have shown that when breast cancer patients with equal numbers of positive nodes are considered there is no statistically significant difference in survival when stratified by the level of positive nodes.

The outcome related to this variable in the present study may have been obscured by another factor. The information concerning the level of the highest positive lymph node was missing in 68% of the studied patients. This fact limits its power in estimating prognosis. On the other hand, we observed a statistically significant association between this variable and percentage of positive lymph nodes. This raises the possibility that any information that could possibly be derived from the level of highest positive lymph node is already represented in the final model by the percentage of positive nodes.

Size of the largest positive lymph node is included in the AJCC staging system as a significant prognostic factor in patients with melanoma metastatic to regional nodes (Table 1). In this review, however, this variable was not significant, even in the univariate analysis. This negative result is strengthened by the fact that this observation was available for 138 (70%) of the patients. Furthermore it must be stressed that patients with very large nodes (in 10 cases measuring more than 5 cm) were included in the study group. Another important finding was that size of the largest node and percentage of positive lymph nodes bear a statistically significant correlation ($r = 0.35$, $p < 0.001$) and we could repeat here the comments already made for the level of highest positive node.

The majority of studies analyzing lymph node-related variables in stage III melanoma have concluded that the number of positive lymph nodes is the most significant prognostic factor.¹⁻⁸ In this study both percentage and absolute number of positive nodes were significant in the univariate analysis. Of these two highly correlated variables ($r = 0.85$), percentage was the more predictive of survival and hence was selected into the final multivariate model.

The analysis of Figure 1, in which the predicted median survival time of four groups of patients is represented, led us to some important conclusions. It clearly indicates that it is possible to predict a very favorable outcome for patients with less than 10% positive nodes, no extranodal disease, and primary lesion at a site other than trunk, independent of primary lesion thickness. It also shows that the prognosis is very poor in patients with extranodal disease and truncal primary lesions, regardless the percentage of positive lymph nodes. Finally it confirms that when the percentage of positive lymph nodes is very high, the prognosis is unfavorable for any combination of those two other significant variables.

The favorable prognosis of patients with clinically negative but histologically positive regional nodes (pathologic stage III and clinical stage less than III) relative to that of patients with clinically and histologically positive regional nodes, has been reported by several authors.^{2,4} In this review we found this to be true only in the univariate analysis. Patients who were clinically staged less than III had a significantly lower percentage of positive nodes. Therefore we must conclude that any possible prognostic advantage in this subset of patients must be associated with a lower tumor burden. Both univariate and multivariate analysis demonstrated the prognostic importance of a low percentage of positive lymph nodes and absence of extranodal disease. In addition to that small number of positive lymph nodes, microscopic disease and negative highest dissected lymph node were also univariately significant. All these elements are indicators of limited regional involvement.

Although this paper was not designed to analyze the timing of ALND, it re-emphasizes the importance of early regional control of the disease, which should be achieved by an elective operation or by short follow-up intervals.²⁵

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Surgical Palliation for Pancreatic Cancer

The UCLA Experience

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We reviewed the records of 340 patients with a tissue diagnosis of pancreatic cancer treated at UCLA Medical Center between 1973 and 1988. Sixty-one patients underwent pancreatic resection (group I), 173 had some form of surgical palliation (group II), and 106 had neither (group III). The diagnosis was made 1 to 2 months more quickly in the last 8 years of the review than in the first 8 years, but the effect of early diagnosis on curability was negligible. Biliary obstruction was best treated by cholecystojejunostomy or choledochojejunostomy, which were equally effective. Anastomoses to the jejunum were safer and more effective than were those to the duodenum for the relief of biliary obstruction. Gastrojejunostomy should be performed prophylactically as well as therapeutically. It was effective and safe in both settings. Surgical palliation for pancreatic cancer was generally effective and was associated with an operative mortality rate of less than 10%. However morbidity was high, with significant complications occurring in one third of cases.

SINCE PANCREATIC CANCER was first described by Montiere in 1836, the apparent global incidence of the disease has increased three or four times.^{1,2} In the United States in 1990, about 27,000 new cases will be diagnosed. Approximately the same number of patients will die of the disease during that period.³⁻⁵ By the time the diagnosis is made, only 10% to 15% of patients with pancreatic cancer are suitable for possible curative resection.⁶⁻⁸ Consequently 85% to 90% of the patients require some form of palliation. The symptoms that most commonly require relief in patients with pancreatic cancer are jaundice, gastric outlet obstruction, and pain. Opinions vary concerning the best approach to the treatment of these problems, as well as their efficacy.

To shed some light on these issues, we reviewed retrospectively a 16-year experience (1973 to 1988) with the palliation of pancreatic cancer at the University of California, Los Angeles (UCLA).

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Methods

From 1973 to 1988, 340 patients with proved tissue diagnoses of pancreatic ductal adenocarcinoma were treated at UCLA. Other pancreatic tumors (*e.g.*, islet cell tumors, cystadenomas, squamous cell carcinomas) as well as cancers of the distal common bile duct, duodenum, and ampulla of Vater, were excluded from the analysis. The hospital charts of all 340 patients were reviewed. Follow-up to the time of death was available on all patients through the UCLA central tumor registry.

There were 185 male (54.4%) and 155 female (45.6%) patients, with a male to female ratio of 1.2 to 1. The patients' ages ranged from 12 to 88 years (mean, 63 years).

We divided the patients into three groups based on the treatment provided (Table 1).

Group I

These patients ($n = 61$, 31 male and 30 female) underwent pancreatic resections. Their ages ranged from 13 to 84 years (mean, 55.5 years). The most common operation was the Whipple pancreaticoduodenectomy (49 patients). Eleven of these were pylorus-preserving resections. Total pancreatectomy and distal pancreatectomy with splenectomy were performed in six patients each. This group was further subdivided according to the year in which the patients underwent surgery. Twenty-two patients were treated between 1973 and 1980 (group IA). Thirty-nine patients were treated between 1981 and 1988 (group IB).

Group II

These patients ($n = 173$, 98 male and 75 female) had procedures to relieve obstructive jaundice and/or gastric

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TABLE 1. *Procedures Performed for Pancreatic Cancer*

Procedure	1973 to 1980	1981 to 1988	Total
Pancreatic resection	22	39	61
Choledochojejunostomy (loop CDJ, 25; Roux-en-Y, 35)	20	40	60
Cholecystojejunostomy (loop CCJ, 48; Roux-en-Y, 26)	25	49	74
Choledochoduodenostomy/ cholecystoduodenostomy	4	12	16
Nonoperative biliary decompression	0	15	15
Gastrojejunostomy alone	2	6	8
Total	73	161	234

outlet obstruction. Their ages ranged from 29 to 85 years (mean, 63 years).

Of the 150 patients who underwent a biliary bypass procedure, 70 (46.7%) also had a gastrojejunostomy performed at the same time. Only eight patients had a gastrojejunostomy without a biliary bypass. Of the 173 patients, 22 (12.7%) had recently undergone a bypass procedure at another hospital before being referred to UCLA. For such patients further surgery at UCLA was limited to revision of the previous bypass procedure. This group was also further subdivided according to the year when the patients underwent surgery. Fifty-one patients were seen between 1973 and 1980 (group IIA). One hundred twenty-two patients were seen between 1981 and 1988 (group IIB).

Group III

The patients in this group ($n = 106$, 56 male and 50 female) had neither resection nor bypass. Their ages ranged from 37 to 88 years (mean, 65 years). Most of them ($n = 71$) underwent a laparotomy but only a tissue biopsy was performed. This was because at the time of the operation there was no evidence of biliary or gastric outlet obstruction requiring bypass. The remaining patients ($n = 35$) in this group were not operated on for a variety of reasons (*e.g.*, advanced age, widespread disease, general ill health, lack of symptoms, patient refusal). In these patients tissue diagnoses were based on percutaneous biopsy of the pancreatic mass or liver metastases, or by biopsy of easily accessible metastatic deposits elsewhere (*e.g.*, in the skin). This group was also subdivided according to the year in which the patients came to the hospital. Fifty patients were seen between 1973 and 1980 (group IIIA). Fifty-six were seen between 1981 and 1988 (group IIIB).

In all the groups, the patient's age and sex, symptoms, the interval between the onset of the symptoms and the diagnosis, and the length of survival were determined. In groups I and II a number of factors related to jaundice were compared. These included preoperative serum bili-

rubin level (highest level and its duration), functional status of the liver, operative mortality (within 30 days of the operation or before discharge from the hospital) and morbidity, the effectiveness of the operative procedure in relieving jaundice clinically (disappearance of color) and biochemically (return of serum bilirubin to normal levels), and the incidence of recurrent jaundice.

In the 80 patients in group II (80 of 150; 53.3%) who underwent biliary bypass alone at their first operation, the incidence of later symptoms of gastric outlet obstruction was determined. Similarly the efficacy, mortality, and morbidity of a gastrojejunostomy performed either alone or with a biliary bypass were assessed. Cholecystojejunostomy (CCJ) and choledochojejunostomy (CDJ) also were compared in regard to efficacy, operative mortality, operative morbidity, recurrence of jaundice, and survival rates. Finally subgroups IA, IIA, IIIA were compared to subgroups IB, IIB, and IIIB to see if the diagnosis was established any sooner in the more recent time period. The effects on survival were analyzed.

Results

The presenting symptoms, their duration, and patient characteristics are summarized in Table 2. Jaundice without pain was seen in only 19% and 19.8% of patients in groups I and II, respectively. Jaundice with pain was seen in 68.9% and 67% of patients in groups I and II, respectively. However in group III, jaundice was infrequent. It was seen in association with other symptoms at some stage of the disease in only 6.6% of cases. Moderate to severe pain, either alone or with other symptoms, was seen in 60.6% and 71.1% of patients in groups I and II, respectively. In group III pain was the chief complaint. It was present in 84% of the patients. Although nausea was seen in the majority of cases, vomiting was unusual. It was seen as the principal symptom in only 3% of the patients in group II and 2% of those in group III.

The diagnosis was made more quickly after the onset of symptoms in two of the groups in the later study period (1981 to 1988) (Table 2). In group I, although the interval was reduced by 4.1 weeks, the difference was not significant. In group II it was reduced by 5.4 weeks and in group III it was reduced by 8.2 weeks ($p < 0.05$ for each).

Information about liver function is shown in Table 3. Liver function was judged abnormal if the concentration of any one of the enzymes (alkaline phosphatase, SGOT, or SGPT) or the total serum bilirubin level was elevated above normal. The highest bilirubin levels were similar in all three groups. In group IA (1973 to 1980), the highest preoperative bilirubin level was 13.5 mg/dL compared to 6.5 mg/dL in group IB (1981 to 1988) ($p < 0.05$); no such differences were seen in groups II and III. Liver function was normal more often in group IB (48.7%) compared to group IA (31.8%) ($p < 0.05$).

TABLE 2. Symptoms in Pancreatic Cancer

Group	Duration Before Diagnosis (Weeks)	Female	Male	Painless Jaundice Alone	Jaundice + Other Symptoms	Pain Alone or with Other Symptoms	Vomiting Alone or with Other Symptoms
IA	13.7	10	12	6/22 27.3%	17/22 77.3%	13/22 59.1%	0 0
IB	9.6	20	19	6/39 15.4%	25/39 64.1%	24/39 61.5%	0 0
I A + B		30	31	19% 6/31	68.9% 25/31	60.6% 18/31	0 0
IIA	17.3*	22	29	3/51 5.9%	36/51 70.6%	38/51 74.5%	1/51 2.0%
IIB	11.9*	53	69	9/122 7.4%	80/122 65.6%	85/122 69.7%	4/122 3.3%
II A + B		75	98	19.8% 19/98	67% 65/98	71.1% 50/70	2.9% 2/70
IIIA	24.1*	23	27	0 0	4/50 8%	44/50 88%	1/50 2%
IIIB	15.9*	27	29	0 0	3/56 5.3%	45/56 80.4%	1/56 1.8%
III A + B		50	56	0 0	6.6% 4/61	84% 51/61	1.9% 1/61

* A versus B $p < 0.05$.

For this and subsequent tables, group I patients are those who underwent pancreatic resections, group II patients are those who had surgical biliary bypass and/or gastric bypass procedures, and group III patients

are those who had only an exploratory laparotomy without bypass or no surgical exploration. A refers to patients treated between 1973 and 1980; B refers to patients treated between 1981 and 1988.

Table 4 lists the results of the various biliary bypass procedures. The jaundice cleared biochemically (*i.e.*, total serum bilirubin returned to normal) in 32%, 42%, and 50% of the CDJ, CCJ, and curative resection patients, respectively. In this regard both resection and the CCJ were more effective than the CDJ ($p < 0.05$). The jaundice cleared clinically (*i.e.*, the skin discoloration disappeared), but the bilirubin did not return to normal in 77%, 74%, and 83.6% of the patients undergoing CDJ, CCJ, and resection, respectively (not significant). The jaundice recurred at some point before the patient died in 13.1%, 13.5%, and 11.5% of the patients undergoing CDJ, CCJ, and resection, respectively (not significant).

An analysis of the patients who developed recurrent jaundice revealed that they had higher preoperative bilirubin levels (17.5 ± 2.6 versus 8.7 ± 2.5 , $p < 0.05$) than the patients in whom jaundice did not recur. Although the patients in whom the jaundice recurred also appeared to be older (65.2 ± 3.4 versus 59.5 ± 3.2 years), have a longer duration of jaundice (4.1 versus 2.4 weeks) and a higher frequency of liver metastases at the time of exploration (55% versus 48%), these differences were not significant.

The mortality rate for patients undergoing CDJ was greater (11.7%) than for those undergoing either a CCJ (5.4%) or resection (4.9%) ($p < 0.05$ for both). For the

TABLE 3. Liver Function in Pancreatic Cancer

Group	Number	Highest Preop. Bilirubin	Duration of Jaundice	Liver Function		Metastases	
				Normal	Abnormal	Yes	No
IA	22	13.5 + 1.9*	2.3 + 0.5	7/22 31.8%	15/22 68.2%	0	22
IB	39	6.5 + 1.3*	1.5 + 0.9	19/39 48.7%	20/39 51.3%	0	39
IIA	51	15.3 + 1.9	3.8 + 0.5 2.9 + 0.9	11/51 21.6%	40/51 78.4%	25/51 49%	26/51 51%
IIB	122	13.8 + 2.5		18/122 14.8%	104/122 85.2%	77/122 63.1%	45/122 6.9%
IIIA	50 (only 4 pts. with jaundice)	16.4 + 4.8	3.4 + 0.4	10/50 20%	40/50 80%	32/50 64%	18/50 36%
IIIB	56 (only 3 pts. with jaundice)	12.8 + 1.4	5 + 1.2	9/56 16.1%	47/56 83.9%	53/56 94.7%	3/56 5.3%

* A vs. B $p < 0.05$.

In group III patients, jaundice was unusual and generally occurred as a terminal event. Liver function was judged abnormal if the following

serum values were exceeded: alkaline phosphatase, 105 U/L; SGOT, 40 U/L; SGPT, 50 U/L; and total bilirubin, 1.2 mg/dL.

TABLE 4. Efficacy of Various Biliary Bypass Procedures

Procedure	Number	Jaundice Cleared		Jaundice Recurred	Mortality Rate	Morbidity Rate
		Biochem.†	Clin.†			
Choledochojejunostomy						
1973-1980	(A) 20	8/20	16/20	2/20	3/20	6/20
		40%	80%	10%	15%	30%
1981-1988	(B) 40	21/40	30/40	6/40	4/40	17/40
		52.5%	75%	15%	10%	42.5%
Cholecystojejunostomy						
1973-1980	(A) 25	11/25	19/25	4/25	1/25	6/25
		44%	76%	16%	4%	24%
1981-1988	(B) 49	20/49	36/49	6/49	3/49	14/49
		40.8%	73.5%	12.2%	6.1%	28.6%
Choledocho- or Cholecystoduodenostomy						
1973-1980	(A) 4	0/4	3/4	0/4	0/4	3/4
		0	75%	0	0	75%
1981-1988	(B) 12	2/12	8/12	4/12	1/12	7/12
		16.7%	66.7%	33.3%	8.3%	58%
Nonsurgical Therapy						
1973-1980	(A) 0	0	0	0	0	0
1981-1988	(B) 15	2/15	4/15	2/15	4/15	10/15
		13.3%	26.7%	13.3%	26.7%	66.7%
Resection						
1973-1980	(A) 22	14/22	19/22	3/22	2/22	3/22
		63.6%*	86.4%*	13.6%	9.1%	13.6%
1981-1988	(B) 39	17/39	32/39	4/39	1/39	8/39
		43.6%*	82.1%*	10.3%	2.5%	20.5%

Jaundice cleared biochemically: cholecystojejunostomy (42%) and Resection (50%), each better than choledochojejunostomy (32%) $p < 0.05$.

Mortality rate: cholecystojejunostomy (5.4%) and Resection (4.9%), each better than choledochojejunostomy (11.7%) $p < 0.05$.

Morbidity rate: cholecystojejunostomy (27%) and Resection (18%), each better than choledochojejunostomy (38.3%) $p < 0.05$.

* For patients undergoing resection, the last serum bilirubin concentration obtained was often at the time of hospital discharge, on average about 2 weeks after operation. At this time the bilirubin level was often

still above normal. Because these patients all eventually became clinically nonjaundiced, the bilirubin measurement was usually not repeated. Thus these values do not reflect accurately the eventual complete normalization of liver function, which was the rule in this group.

† Biochemical clearing of jaundice meant that the total serum bilirubin concentration decreased to 1.2 mg/dL or less. In other patients the jaundice cleared clinically, *i.e.*, the yellow discoloration disappeared even though the serum bilirubin concentration may still have been elevated above this value.

same procedures the frequency of serious morbidity was 38.3%, 27%, and 18%, respectively ($p < 0.05$ for CDJ *versus* CCJ and resection) (Table 5). Patients in whom the duodenum was used (either a choledochoduodenostomy or a cholecystoduodenostomy) for biliary bypass suffered complications (usually sepsis, failure to clear jaundice, or recurrence of jaundice) in 63% of cases ($p < 0.001$ *versus* all other operative procedures).

Nonoperative biliary decompression was used in 15 patients as definitive treatment in the later study period (1981 to 1988)(Table 4). In this small group, jaundice cleared biochemically in 13.3%, clinically in 26.1%, and recurred in 13.3%. The mortality rate was 26.7% and the morbidity rate 66.7%. Both the mortality and morbidity rates were significantly greater than for the operative procedures ($p < 0.005$).

Gastrojejunostomy was performed in 70 of the 150 patients (46.7%) undergoing biliary bypass. Of these, 50 of these procedures were performed for either actual or imminent gastric outlet obstruction and 20 were performed prophylactically. Of these 70 gastrojejunostomies, two

(2.9%) failed completely. Nine (12.9%) took longer than 20 days to function. Three patients (4.3%) required re-exploration after 2 weeks. Thus overall 20% of these patients had some problems. Of the eight patients who underwent gastrojejunostomy as the sole procedure, one gastrojejunostomy failed to function for 30 days. The remaining gastrojejunostomies functioned within 10 days. Of the 80 patients who underwent biliary bypass alone, 20 (25%) required a gastrojejunostomy later (from 10 days to 24 months after the biliary bypass). All of them functioned within 10 days. An additional 19 (23.9%) of these 80 patients undergoing biliary bypass alone developed marked nausea and vomiting in the terminal stages of their disease. However none of these patients, because of their frailty, had investigations to exclude gastric outlet obstruction as the cause. They were managed with either nasogastric suction or total parenteral nutrition until they died.

Survival for the various groups is summarized in Tables 6 and 7. As expected the overall survival for group I (19.5 ± 2.6 months) was greater than for group II (8.0 ± 0.7

TABLE 5. Morbidity of Various Operations for Pancreatic Cancer

Complication	Cholecysto(doch)- Duodenostomy (16 pts)	Cholecysto- Jejunostomy (74 pts)	Choledoch- Jejunostomy (60 pts)	Resection (61 pts)
Cholangitis	4	7	5	0
Wound infection	2	4	2	0
Pneumonia	1	2	3	2
Bacteremia	1	1	0	0
Wound dehiscence	0	1	0	0
Small bowel obstruction	0	2	0	0
Cardiac (MI, Failure)	0	2	4	0
Abscess	0	0	2	4
Hemorrhage	0	0	2	3*
Fistula	0	0	1 (Bile)	4*
Renal failure	0	0	2	1
Thrombophlebitis	0	1	3	0
Ischemic small bowel	0	0	0	2
Reoperation	2 (13%)	1 (1%)	5 (8%)	7 (11%)
No. complications/No. pts	10 in 10 pts	20 in 20 pts	24 in 24 pts	16 in 11 pts
Complication rate	10/16 (63%)	20/74 (27%)	24/60 (40%)	11/61 (18%)

* Hemorrhage: 2 from gastrojejunostomy suture line, 1 from portal

vein; all required reoperation; Fistula: all from the pancreaticojejunostomy; none required reoperation.

months) ($p < 0.005$) and group III (4.6 ± 1.1 months) ($p < 0.001$). In group I, the survival time was significantly longer in the later period of the study (1981 to 1988) (22.1 versus 16.2 months) ($p < 0.05$). However there were no significant differences in survival times for groups II (7.8 versus 7.1 months) and III (4.5 versus 4.8 months) in the two time periods. In group II patients undergoing a CDJ alone survived 6.8 ± 2.8 months compared to 6.1 ± 2.0 months when a gastrojejunostomy was added (not significant). Similarly those patients undergoing CCJ alone survived 8.6 ± 2.7 months compared to 9.6 ± 4.6 months when a gastrojejunostomy was also done (not significant).

Discussion

Symptomatology

At UCLA, over a period of 16 years (1973 to 1988 inclusive), we saw 340 patients with a tissue diagnosis of adenocarcinoma of the pancreas. Although often described as a presenting symptom in the disease, painless jaundice was uncommon (group I, 19%; group II, 6.9%). More often jaundice was associated with other symptoms, especially pain. It was seen in about 70% of both the group I and group II patients. Similar figures have been reported

by others.⁹⁻¹² Jaundice was less common in group III patients (in only 6.6% of cases). Indeed the diagnosis might have been arrived at earlier in this group if jaundice had been present more frequently. When it did appear, it was a terminal event in association with gross hepatic infiltration by the tumor. Pain was the major symptom in 61%, 71.7%, and 84% of the patients in groups I, II, and III, respectively. The patients in groups I and II complained mainly of intermittent upper abdominal colicky pain. In group III the pain was more often constant and it was felt in the back as well as the upper abdomen. Thus the characteristics of the pain of pancreatic cancer seemed to alter as the disease advanced and back pain seemed to correlate with unresectability.

Diagnosis

The interval between the first symptoms and the establishment of the diagnosis has attracted considerable attention. Efforts to shorten this interval have been stimulated by the hope that earlier diagnosis would result in increased resectability and survival rates. In 1970 Beall et al.¹³ found this interval to be 18 weeks. Andersson et al.¹⁴

TABLE 6. Overall Survival Statistics

Group	Number	Total Group Survival (months)
IA	22	16.2 + 4.1
IB	39	22.1 + 3.3
IIA	51	7.8 + 1.1
IIB	122	7.1 + 0.8
IIIA	50	4.5 + 0.9
IIIB	56	4.8 + 0.6

TABLE 7. Survival Data for Nonsurgically Palliated Group III Patients

	Laparotomy	No Laparotomy	Total
1973-1980 (A)	30 pts.	20 pts.	50 pts.
Survival (months)	3.9 + 0.9	4.8 + 0.8	—
1981-1988 (B)	41 pts.	15 pts.	56 pts.
Survival (months)	4.1 + 0.5	4.9 + 0.7	—
Death from			
Hepatic Failure	27/71 (38%)	13/35 (37.1%)	—
Multiorgan Failure	40/71 (56.3%)	19/35 (54.3%)	—
Myocardial Failure	4/71 (5.6%)	3/35 (8.6%)	—

in 1976 found the interval to be 14 weeks for carcinoma of the head of the pancreas and 22 weeks for carcinoma of the body and tail. At UCLA this interval varied among the three groups and especially between the two time periods of the study (1973 to 1980 *versus* 1981 to 1988). In group I patients, those who underwent resection, it was not reduced significantly. Nevertheless the preoperative bilirubin levels for group IA were higher than for group IB (13.5 *versus* 6.5 mg/dL, $p < 0.05$), which suggested that the disease was being treated at an earlier stage. In groups II and III patients, the time to diagnosis was reduced by 5.4 weeks to 11.9 weeks and by 8.2 weeks to 15.9 weeks, respectively ($p < 0.05$ for both groups II and III). With this the resectability rate increased from 13.8% in group IA to 21.5% in group IB ($p < 0.05$). Conversely the proportion of patients who were offered neither resection nor palliation decreased from 40.1% (65 of 159 patients) in group IIIA to 22.7% (41 of 181 patients) in group IIIB ($p < 0.05$).

Jaundice

Much discussion has centered on the ideal surgical procedure for the relief of jaundice. There is general agreement that jaundice should be relieved as early as possible. Prolonged jaundice impairs liver function and this may lead to liver failure. Indeed 38% of group III patients (nonpalliated) died with a variety of problems related to the liver (increasing jaundice and pruritus, recurrent cholangitis and/or liver failure). Jaundice is associated also with anorexia and malabsorption, which may lead to malnutrition. Pruritus, usually difficult to control with drugs, has been reported in 25% of patients by Baker et al.¹⁵ In the present series pruritus was seen in 20.6% of patients with jaundice. Finally persistent jaundice is an unpleasant reminder to both the patient and his or her family of the uncontrolled nature of the disease.

Choledochojejunostomy and Cholecystojejunostomy

Comparisons have been made before between a CCJ and CDJ. Deschamps et al.¹⁶ reported that the jaundice failed to clear in 25% of their patients who underwent CCJ compared to 10.3% of those undergoing CDJ. The mortality rates were 10% and 7%, respectively, for the two operations. They favored the use of the common bile duct for relief of the biliary obstruction. Blievernicht et al.¹⁷ also reported a higher recurrence rate for jaundice in their patients who underwent CCJ as opposed to CDJ. However Sarr et al.¹⁸ in their extensive review of the literature could find no advantage to the CDJ compared to the CCJ.

Our results (Table 4) also showed no difference in efficacy between the two operations. The frequency with which jaundice was relieved both biochemically and clinically was similar for both, as were the recurrence rates for jaundice. However the mortality and morbidity rates

when the common duct was used for the bypass were greater than they were in those undergoing CCJ (11.7% *versus* 5.4% mortality, and 38.3% *versus* 27% morbidity, respectively; $p < 0.05$). Although one might postulate that the patients who had a CDJ had more advanced disease, a larger tumor, a longer operation with more blood loss, and so on, we found no evidence for these factors. Thus the reasons for the differences in mortality and morbidity rates were not apparent from this retrospective analysis.

In general we recommend a CCJ because it is effective and generally can be done more quickly and easily. Of course the concern about the use of the gallbladder to relieve obstructive jaundice is appropriate. When the tumor has involved the distal common bile duct, the cystic duct/common duct junction may be obstructed, or it may become obstructed as the tumor grows. Then a CCJ would not be effective, and a CDJ is indicated. For that reason it is important to ensure cystic duct patency visually and/or by an operative cholangiogram before using the gallbladder for decompression.

Choledcho/cystoduodenostomy

We used the duodenum infrequently for biliary bypass because of the concern that the anastomosis would lay too close to the tumor. With subsequent spread of the tumor to that area, jaundice could recur. Indeed jaundice persisted more often (33%) and recurred more frequently (33%) when the duodenum was used compared to when the jejunum was used (Table 4). Major postoperative morbidity occurred in 63% of the patients. It is unclear why others have had more success with this operation. For example the Cleveland Clinic group¹⁹ recently reported their results in which choledochoduodenostomy apparently provided excellent palliation. Nevertheless such opinions are few and we recommend anastomoses to the jejunum instead. They can be performed safely and easily in most instances, and reobstruction is less likely. A loop jejunostomy without a jejunojejunostomy is satisfactory. In the occasional patient in whom a long survival might be anticipated, a Roux-en-Y jejunostomy may be preferred.

Nonoperative biliary drainage (endoscopic or percutaneous transhepatic stenting) was used only as definitive treatment for jaundice in the later period (1981 to 1988). It was associated with higher rates of recurrent jaundice, mortality, and morbidity compared to operative biliary bypass, and the jaundice cleared clinically in only 25% of the cases. However this form of palliation was reserved for the poorest-risk patients. Therefore our experience should not be interpreted as a condemnation of this approach. More recent studies suggest that endoscopic stenting to relieve obstructive jaundice from perampullary tumors can be a safe and effective alternative to surgical bypass in selected patients.²⁰

A total of 61 patients (group I) underwent pancreatic

resection in an attempt to cure the pancreatic cancer. Because the majority of these patients eventually died with recurrent disease, in retrospect most of these procedures were also palliative in nature. In that regard these operations were quite effective. The jaundice resolved clinically in about 85% of these patients by the time they were discharged from the hospital. It recurred usually just before death in about 10% of cases. The overall mortality rate for pancreatic resection was 4.9%, and in the years 1981 to 1988 it was only 2.5% (1 of 39 patients). Nevertheless it is important to stress that we do not advise pancreatectomy in patients in whom cure does not appear to be possible.

Gastrojejunostomy

Doberneck et al.²¹ reported their experience with gastrojejunostomy in pancreatic cancer. They found that delayed gastric emptying (inability to tolerate oral fluids by the eighth postoperative day) complicated the recovery of 26% of their patients who had no preoperative evidence of duodenal obstruction and 57% of those who did. They believed that the resultant prolongation of hospital stay negated any putative benefits of the procedure. Weaver et al.²² recently reviewed their experience with gastrojejunostomy and found that the operative mortality rate in their patients varied from 40% to 90%. They questioned its value under any circumstances.

Our experience has been more encouraging than that related in either of these reports. At UCLA 70 patients had combined biliary bypass and gastrojejunostomy. The procedure was prophylactic in 20 and therapeutic in 50 patients. The mortality rates were similar in the two groups (5% and 12%, respectively). Although the overall morbidity rate was 20% and reoperation was needed in 3 patients, 68 of these 70 gastric bypasses eventually functioned. Of the 80 patients who underwent biliary bypass alone, 20 (25%) required a gastrojejunostomy from 10 days to 24 months later. All of these functioned within 10 days. Unfortunately we could find nothing to suggest that their eventual obstruction should have been predicted earlier in this group of patients. There were no differences in survival rates between patients undergoing a CDJ or CCJ alone or one of these procedures combined with a gastrojejunostomy. The operative mortality rates were also similar whether a biliary bypass procedure was combined with a gastrojejunostomy (8.6% with and 6.3% without).

For all of these reasons, we think that a gastrojejunostomy should be performed in almost all patients who undergo a biliary bypass and are expected to live beyond a few weeks. If possible an antecolic gastrojejunostomy, distal to the biliary bypass, should be used. Although it is unusual, a retrocolic anastomosis is more likely to become involved by tumor invading the transverse mesocolon.

Pain

The etiology of pain in pancreatic cancer is unclear, but a number of possibilities have been suggested. Some believe that pancreatic and common bile duct obstruction produce ductal hypertension and this causes pain. This is the rationale for pancreatic ductal decompression in patients with pancreatic cancer, a technique that has not been widely practiced.²³⁻²⁶ We have not performed this procedure, although a rigorous study of its efficacy has not been done.

However of those patients who underwent a palliative biliary bypass (which would have relieved biliary ductal hypertension), less than 10% reported any noticeable relief from pain after surgery. Even in those patients whose pain was improved, it invariably recurred within a few weeks to months after operation.

Invasion of the pancreatic and peripancreatic nerves (visceral and somatic) may be another cause of pain in these patients. Many ablative procedures have been described in an effort to relieve pain. These include individual resection of the greater, lesser, or least splanchnic nerves,²⁷⁻²⁹ celiac and superior mesenteric ganglionectomy,³⁰ and division of the post ganglionic fibers from the celiac plexus.³¹ None of these procedures has been used at UCLA. However we have had some experience with intraoperative destruction of the celiac ganglia. This has been done by injecting 20 to 30 mL of 50% ethanol into either side of the aorta in the region of the ganglia. Of 30 patients treated in this way, 19 (63.3%) had abolition or significant reduction in their pain for 1 to 4 months. In the remaining 11 (34.7%) the procedure failed. Either there was no pain relief or the pain returned within a few days. Other authors also have found this procedure useful.³²⁻³⁴ It is associated with minimal morbidity (none in the present series), and if the intraoperative attempt fails, a percutaneous approach can be used by an anesthesiologist at a later date. Nevertheless a controlled study of its efficacy is needed.³⁵

Survival

In groups II and III, despite more rapid diagnosis, there was no improvement in survival from the early period to the later one. This was not the case for group I patients who lived an average of 6 months longer after pancreatic resection in the later time period (16.2 ± 4.1 versus 22.1 ± 3.3 months, $p < 0.05$). The explanation for this improved survival is not clear. It is unlikely to be due to earlier diagnosis because there was statistically no difference in the time to diagnosis in this group.

Table 7 summarizes the fate of those patients who were not palliated (group III). More than one third of them died primarily from hepatic failure and more than one half from multiple-organ failure. The patients have been

subdivided into those who underwent laparotomy and those who did not. The causes of death and survival times were similar in the two subgroups. This suggests that laparotomy might be avoided in those patients in whom both the diagnosis and unresectability of the cancer are certain, and in whom jaundice and/or duodenal obstruction do not require operative relief.

We reviewed the records of 340 patients with pancreatic cancer treated at UCLA from 1973 to 1988. In the last half of the study, the diagnosis was made up to 2 months sooner than in the first half. This was associated with a higher resectability rate (13.8% *versus* 21.5%), and fewer patients with disease so far advanced that no palliative treatment could be offered (40.1% *versus* 22.7%). For relief of obstructive jaundice, CCJ and CDJ were equally effective (75%). However the use of the common duct was associated with slightly higher mortality and morbidity rates. In our experience, the duodenum was less satisfactory to decompress the obstructed biliary tree. Mortality and morbidity rates were high and the jaundice recurred in one third of cases. Gastrojejunostomy was safe and effective in most cases. It should be done in all patients, even if gastric outlet obstruction is not present at the time of exploration. If it is not done, at least 25% of patients will require a second operation to relieve the obstruction that develops as the tumor grows. Patients undergoing pancreatic resection for attempted cure have experienced an average increase in survival of about 6 months during the last half of the study. This does not appear to be due to earlier diagnosis.

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Radical Pancreatectomy for Pancreatic Cancer in the Elderly

Is it Safe and Justified?

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Surgical resection provides the only potential cure for pancreatic cancer, yet resection in patients 70 years of age and older remains controversial because of presumed increased morbidity and mortality. Our aim was to determine the operative results in patients 70 years of age or older undergoing potentially curative radical pancreatic resection for pancreatic cancer from 1982 through 1987. Of 206 consecutive patients explored for potential resection, 42 patients (mean age, 75 years) had potentially curative procedures, including radical pancreaticoduodenectomy in 23 patients, total pancreatectomy in 8 patients, and distal pancreatectomy in 11 patients. Ductal adenocarcinoma was the most frequently encountered neoplasm (69%), but cystadenocarcinoma and islet cell carcinoma accounted for 12% and 7%, respectively. The overall operative mortality rate was 9%, while surgical morbidity was 28%, and medical morbidity was 12%. Overall median survival was 19 months, and 5-year survival was 4%. Despite the low overall incidence of resectability and postoperative cure rate for pancreatic carcinoma, exploration for potential curative resection should not necessarily be withheld for healthy, selected patients who are older than 70 years. Morbidity and mortality rates, although slightly greater than for patients who are older than 70 years, are acceptable.

SURGICAL EXCISION OFFERS the only potential cure for pancreatic malignancy. However the efficacy and rationale for radical pancreatic resection in the treatment of pancreatic neoplasia has been questioned by some investigators given the high operative mortality rates and dismal long-term survival rates reported in the past.^{1,2} The magnitude of this controversy is even greater for patients 70 years of age and older^{3,4} for several reasons. First the peak incidence of pancreatic neoplasia occurs in the sixth and seventh decades of life, and second, as the average duration of life expectancy continues to increase,

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an increasingly older population is at greater risk for developing pancreatic cancer. These factors may magnify the already-increasing incidence of pancreatic cancer.

Recommendations regarding the appropriate treatment of pancreatic cancer in the elderly remain based on surgical experience reported in the distant past and may not be unjustified. More recently surgeons from many centers worldwide with an interest in and experience with surgery for pancreatic cancer have reported markedly decreased morbidity (less than 30%) and mortality rates (less than 5%) after radical pancreatic resections for pancreatic cancer. Furthermore there has been a suggestion that long-term survival may be increased as well for reasons that are unknown.⁵⁻⁸ Currently most pancreatic surgeons believe that major pancreatic resection should be performed with an overall mortality of less than 5%. Indeed, if documentation of reduced perioperative morbidity and mortality can be confirmed in the elderly, such treatment should not be withheld solely on the basis of age. With these concepts in mind, we have reviewed our experience with major pancreatic resection for all types for pancreatic neoplasia during a recent 5-year interval. Our intent was to determine the perioperative morbidity and mortality rates of radical pancreatic resection in patients who are 70 years of age or older.

Clinical Material

The medical records of all consecutive patients aged 70 years or older undergoing exploration for all biopsy-proved primary pancreatic malignancy between 1982 and 1987 were reviewed. This time period was selected as recent reports⁵⁻⁸ have suggested improved trends in perioperative morbidity and long-term (5-year) survival in

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current surgical practice. These patients were considered to have resectable lesions based on physical examination and radiologic investigation; all were deemed fit to tolerate a major surgical procedure based on performance status. Performance status was estimated by impairment of physical activity as noted by the American Cancer Society, Eastern Cooperative Oncology Group (ECOG). Scores of 0 to 4 are assigned as to the degree of impairment, with 0 = unrestricted, 1 = restriction from strenuous physical activity, 2 = capable of self care, 3 = confined patients, and 4 = invalid patients. Of the patients undergoing curative resection, all but one patient were ECOG class 0 and 1; one patient who had undergone abdominal exploration without resection elsewhere was ECOG class 3. Curative resection was defined as resection of all known tumor with pathologically confirmed free margins. Multiple clinical variables were abstracted from each record to define the clinical presentation and to concentrate on the perioperative morbidity and mortality. Follow-up data concerning survival was obtained in all patients who had undergone curative resections, either by telephone contact with the patient or with next of kin if the patient had died. Death certificates were reviewed if available. Because of the retrospective nature of this study, meaningful data on the important topic of quality of life, such as long-term morbidity related to pancreatectomy, maintenance of pain relief, and so on, could not be determined. Of the 164 patients that had palliative procedures or exploration only, follow-up was available in 66% of patients through our cancer registry.

Results

Patient Characteristics

During this 6-year period (January 1982 through December 1987), 206 patients aged 70 years or older underwent exploration for potential resection of biopsy-proved primary pancreatic tumors. Palliative biliary and/or gastric bypass was performed in 118 patients, while 46 patients with unresectable disease were explored with biopsy only; the 42 remaining patients were found to have resectable lesions and underwent a pancreatic resection

TABLE 1. Presenting Symptoms in Patients ≥ 70 Years Old Undergoing Radical Pancreatic Resection for Malignancy

Symptom	Percentage
Weight loss	31
Jaundice	20
Abdominal pain	18
Steatorrhea	10
Anorexia/nausea	9
Generalized fatigue	7
Pruritis	4
Asymptomatic	1

TABLE 2. Histopathology of Pancreatic Resections in Patients ≥ 70 Years Old

Histopathology	Number (%)
Ductal adenocarcinoma	28 (68)
Cystadenocarcinoma	6 (13)
Islet cell carcinoma	3 (7)
Ampullary carcinoma	2 (5)
Squamous cell carcinoma	2 (5)
Carcinosarcoma	1 (2)
Total	42

with curative intent (overall resectability rate in patients aged 70 years or older, 21%). These latter 42 patients constituted the study group in this report.

The mean age of the patients undergoing curative resection was 75 years; seven patients were older than 80 years, and the oldest patient was 85 years of age. There were 22 men and 20 women. The most common presenting symptoms were weight loss, jaundice, and pain (Table 1). Patient presentation was similar to that in younger patients, with weight loss of more than 5 pounds the most frequent symptom (30%). The mean duration of symptoms was 6 weeks. Laboratory evaluation revealed hyperbilirubinemia (more than 2.0 mg/dL) in 55% of patients, while alkaline phosphatase and serum glutamylxyl transferase were each elevated in approximately one third of the patients before operation.

Pathologic Characteristics

The most frequently encountered neoplasm was ductal adenocarcinoma (69%); islet cell carcinoma, ampullary cancer, cystadenocarcinoma, adenoacanthoma, and carcinosarcoma comprised the remaining malignancies (Table 2). Neoplasms involved the periampullary region or head of the pancreas in 31 patients. Radical pancreaticoduodenectomy was performed in 23 patients, four of whom had a pyloric-preserving modification of that procedure. The mean operative time was 5.5 hours. Eight patients underwent total pancreatectomy because the resection margins were positive after radical pancreaticoduodenectomy or both pancreatic endocrine and exocrine insufficiency were present before operation. The mean operative time for total pancreatectomy was 6 hours. The remaining 11 patients had tumors confined to the body of the gland and underwent radical distal pancreatectomy with a mean operative time of 4.75 hours.

Mortality and Morbidity

Operative mortality. The operative mortality, defined as death before discharge or within 30 days of operation, was 9% (four patients). Their ages were 72, 75, 76, and 77 years. One patient died suddenly of a pulmonary em-

bolus just before discharge after an otherwise uncomplicated postoperative course. The other three patients had complicated postoperative courses. One patient developed a leak at the choledochojejunostomy and another had a leak from a gastrostomy tube; both developed sepsis and required reoperation for drainage of intra-abdominal abscesses; they eventually died of multiple-organ failure on the 41st and 11th postoperative days, respectively. The third patient had undergone choledochoduodenostomy and distal pancreatectomy elsewhere for complications believed to be secondary to pancreatitis. Review of the surgical specimen revealed ductal adenocarcinoma, and he was re-explored and underwent a completion total pancreatectomy. After operation he developed portal vein thrombosis and eventually died of liver failure. Thus three deaths occurred after pancreatoduodenectomy, and one followed a completion total pancreatectomy. Overall operative mortality rate for resection of lesions in the pancreatic head was 12% (4 of 31 patients) and for distal lesions was 0% (0 of 11 patients).

Operative morbidity. Overall morbidity rate was 31%. Significant surgical morbidity related to the technical aspects of the procedure, including hemorrhage, sepsis presumed related to the pancreaticojejunostomy or the pancreatic closure, gastric or biliary leakage, or postoperative small bowel obstruction occurred in 28% of patients overall. Medical morbidity, including respiratory failure requiring ventilatory support, renal failure requiring temporary dialysis, pulmonary embolus, myocardial infarction, and hepatic failure occurred in 12% of patients (Table 3). The median duration of hospitalization was 16 days, with a median stay in the intensive care unit of 2 days.

Survival

Median overall survival time was 19 months, and 1-year and 5-year survival rates were 66% and 4%, respectively. Median survival time in the patients with ductal adenocarcinoma, the most commonly encountered neoplasm, was 18 months, although two patients have survived for more than 5 years. In addition eight patients are alive at a mean of 33 months, six of whom had ductal adenocarcinoma. In contrast with the above, survival time

in the patients who underwent a nonresective procedure was only 5.5 months; meaningful comparison between these groups, however, cannot be made.

Discussion

Our study demonstrated that major curative pancreatic resection in selected healthy patients who are 70 years old or older with pancreatic cancer can be carried out with satisfactory results. The operative morbidity (31%) and mortality (9%) rates are somewhat greater than our previously reported results with resection in patients of all ages.⁹⁻¹¹ These factors must be considered when contemplating resection in the elderly; nevertheless surgical resection offers the only potential procedure for long-term survival.

Reluctance to undertake radical pancreatectomy stems from past reports of prohibitive operative morbidity and mortality, each exceeding 40%,^{12,13} and from opinions of physicians and surgeons alike that geriatric patients tolerate resection less well than do younger patients.¹⁴ Recently many institutions have reported markedly decreased operative morbidity (less than 40%) and mortality (less than 5%) rates after major pancreatic resection for primary pancreatic malignancy.^{5,6,8,12} Furthermore several recent reports have suggested an increase in long-term survival (5-year survivals approaching 15%) after curative pancreaticoduodenal resection for ductal adenocarcinoma^{5,6,8} and especially with adjuvant radiotherapy.⁷ However these reports did not specifically attempt to address or define operative risk factors for radical pancreatectomy in the elderly (patients older than 70 years) as a subgroup. With the continued increase in our geriatric population and increased incidence of pancreatic cancer in the elderly, and with the increasing overall incidence of pancreatic cancer over the last several decades,¹⁵ appropriate treatment of elderly patients with a pancreatic neoplasm becomes an important consideration. Our results, and those of Kairaluoma and colleagues,¹⁶ support the contention that age alone should not necessarily be a limiting factor for a potentially curative pancreatic resection. Although our study was not designed to investigate the quality of life after resection or to compare survival

TABLE 3. Postoperative Morbidity in Patients ≥ 70 Years Old Undergoing Radical Pancreatic Resection for Malignancy

Surgical	Number (%)	Medical	Number (%)
Hemorrhage	9 (19)	Respiratory failure	2 (5)
Sepsis	7 (16)	Renal failure	2 (5)*
Biliary leak	4 (9)	Pulmonary embolus	2 (5)
Gastrostomy leak	1 (2)	Myocardial infarction	1 (2)
Small bowel obstruction	1 (2)	Hepatic failure	1 (2)
Total	12 (28)	Total	5 (12)

* Requiring temporary hemodialysis.

in patients resected *versus* comparable patients who underwent only a palliative procedure,¹ we believe that attempts at curative resection are justified. Others have reported that resection improves palliation and prolongs survival.⁸ The median survival time in our elderly population after resection was 19 months, and 66% of patients survived for 3 years. Furthermore two patients with ductal adenocarcinoma survived for more than 5 years without evidence of disease, which implies a cure of their malignancy. Nonresective surgical palliation in these patients would have prevented this possibility for prolonged survival.

Obviously we have not excluded elderly patients from curative resection on the basis of age alone in the past. Indeed a previous study from our institution in patients undergoing all forms of operative therapy showed that age alone was not necessarily a major predictive factor in operative mortality.¹⁷ Today we continue to advocate an aggressive approach toward resection in selected patients aged 70 years or older who have pancreatic cancer. The characteristics of the patient population who underwent resection in our study make this a select group. All were medically fit and all but one were of a satisfactory performance status (ECOG class 0 or 1). Despite preoperative findings that suggest less advanced, localized disease at the time of exploration, only 21% proved resectable. This was not unexpected given the many ductal adenocarcinomas. Of the four patients who died after operation, pre-existing medical conditions were not apparent deciding factors in their deaths. The predominant complication was sepsis related to biliary or enteric leaks after pancreatoduodenectomy and total pancreatectomy (three patients). One additional patient had an uncomplicated postoperative course but died of a fatal pulmonary embolus just before discharge. Whether these complications or the host's ability to deal effectively with the sequelae can be attributed to advanced age is unknown.

Operative morbidity and mortality rates in patients older than 70 years are somewhat greater than in younger patients undergoing major pancreatic resection.⁹⁻¹¹ However results are acceptable and survival time appears to be increased. Despite the low incidence of resectability

and the dismal long-term prognosis without resection, major pancreatic resection should not necessarily be withheld for medically healthy patients who are older than 70 years.

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Current Management of the Budd–Chiari Syndrome

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Twenty-six patients with the Budd–Chiari syndrome were treated surgically at the Johns Hopkins Hospital. Twenty-one of the patients were female and five were male, with a median age at diagnosis of 37 years. Nine patients had polycythemia vera, 6 were receiving estrogen therapy, 5 had a previous hepatitis A or B infection, and 4 had cirrhosis. There was one case each of hepatic malignancy, paroxysmal nocturnal hemoglobinuria, and idiopathic thrombocytopenic purpura. In five cases no etiologic factors or associated disorders were identified. Ascites was the most common presenting feature in this group of patients. Hepatic function at the time of diagnosis, as measured by standard serum chemistries, was only minimally abnormal. The diagnosis of the Budd–Chiari syndrome was confirmed in all 26 patients by hepatic vein catheterization. Inferior vena cavography was also performed and revealed caval occlusion in 4 patients, significant caval obstruction in 13 patients, and a normal vena cava in 9 patients. Interpretation of the vena cavaogram was helpful in selecting the appropriate surgical procedure for each patient. Twenty-three of the twenty-six patients underwent percutaneous liver biopsy before operation, with no morbidity or mortality. Four patients had well-established cirrhosis noted on biopsy. Thirty mesenteric-systemic venous shunts were performed on the 26 patients. In 11 patients a mesocaval shunt was performed and in one instance conversion to a mesoatrial shunt was required as a second procedure. In 15 patients a mesoatrial shunt was performed as the initial procedure. Graft thrombosis occurring in 2 of these 15 patients prompted one revision in 1 patient and 2 revisions in the second patient. After mesenteric-systemic venous shunt, eight of the patients (31%) died before discharge from the hospital. The remaining 18 patients in this series were discharged from the hospital alive and well with patent shunts. Patients were followed for a median of 43 months (range, 9 months to 13 years). Five late deaths occurred between 5 and 84 months after the operation. Three- and five-year actuarial survival rates were 65% and 59%, respectively.

THE BUDD–CHIARI syndrome is a rare, often fatal illness resulting from hepatic venous outflow occlusion. The obstruction may be due to throm-

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bosis of the major hepatic veins or suprahepatic vena cava or, as is more common in the Orient, membranous obstruction of the suprahepatic inferior vena cava.¹ Patients with hepatic venous congestion secondary to the Budd–Chiari syndrome present with manifestations of portal hypertension (ascites and/or bleeding esophageal varices), which may develop either acutely or chronically. A number of surgical procedures have been suggested to decompress the congested liver by converting the portal vein into an outflow tract.^{2–8} Portacaval, mesocaval, or mesoatrial shunts have all been used successfully. Orthotopic liver transplantation is now an option in managing the Budd–Chiari syndrome and selected patients can expect the most favorable outcome with this form of therapy.^{9,10} We report here experience with 26 patients with the Budd–Chiari syndrome who were treated surgically at the Johns Hopkins Hospital during a 15-year period. Based on this experience we have developed a treatment regimen that should result in successful management of most patients with this otherwise fatal syndrome.

Clinical Material

Between 1973 and 1988, 26 patients with the Budd–Chiari syndrome were treated surgically at the Johns Hopkins Hospital. Twenty-one were women and five were men (Table 1). The median age at the time of diagnosis was 37 years (range, 14 to 68 years) and the median duration of symptoms prior to evaluation at the Johns Hopkins Hospital was between five and six months (range, 1 week to 5 years). Twenty-four of the 26 patients were found to have ascites at the time of diagnosis and in most cases the ascites developed over a period of weeks or

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TABLE 1. *Epidemiologic Factors in 26 Patients with Budd-Chiari Syndrome*

Factor	Mesocaval Shunt	Mesoatrial Shunt	Both
Age	32 years	40 years	37 years
Sex	9F/2M	12F/3M	21F/5M
Race	9W/2B	12W/3B	21W/5B
Symptom duration at diagnosis	6 months	5 months	5.5 months

months. Abdominal pain or discomfort, always mild, was present in 42% (11 of 26) of our patients. Jaundice was clinically evident in 27% (7 of 26) and gastrointestinal bleeding was documented in five patients (19%).

Of the etiologic factors known to be associated with the Budd-Chiari syndrome, polycythemia vera (35% or 9 patients) and estrogen use (23% or 6 patients) were most commonly recognized. Five of the twenty-six patients (19%) had previously documented episodes of infectious hepatitis and four patients (15%) were known to have cirrhosis at the time of diagnosis. Paroxysmal nocturnal hemoglobinuria, idiopathic thrombocytopenic purpura, and hepatic malignancy were each present in one patient. Five patients (19%) had no identifiable predisposing or associated factors for the Budd-Chiari syndrome and were categorized as idiopathic (Table 2).

At the time of admission the median serum bilirubin was 1.4 mg/dL (range, 0.6 to 25.0 mg/dL), median SGOT was 39 IU/L (range, 11 to 9480 IU/L), median SGPT was 22 IU/L (range, 14 to 6710 IU/L), and median alkaline phosphatase was 136 IU/L (range, 44 to 326 IU/L). Mild elevation of the prothrombin time was noted, with a mean value of 13.8 seconds (range, 11.5 to 19.7 seconds).

All patients were evaluated by catheterization and imaging of the hepatic veins. The diagnosis of the Budd-Chiari syndrome was confirmed by demonstrating completely occluded hepatic veins or recanalized veins with the typical 'spider web' appearance. The inferior vena cava was also evaluated angiographically, the results of which

TABLE 3. *Results of Preoperative Inferior Vena Cavography Among 26 Patients with the Budd-Chiari Syndrome*

Result	Mesoatrial Shunt	Mesocaval Shunt
Caval occlusion	4/15 (27%)	0
Significant caval obstruction (compression >75% or gradient >20 mmHg)	11/15 (73%)	2/11 (18%)
No significant caval obstruction	0	9/11 (82%)

are shown in Table 3. Total caval occlusion was demonstrated in four patients. Significant caval obstruction, as demonstrated by more than 75% reduction of luminal diameter by extrinsic compression or intracaval thrombus, or a pressure gradient across the compressed cava exceeding 20 mm of mercury, was present in 13 patients. No significant caval obstruction was observed in nine patients.

Percutaneous liver biopsies were performed before operation on 23 of the 26 patients. Despite the presence of ascites and a mild coagulopathy, there was no morbidity or mortality from these procedures. The histopathologic picture most often associated with the Budd-Chiari syndrome was centrilobular congestion. The spectrum of this pathology ranged from sinusoidal dilatation with variable amounts of red cell extravasation to hepatocellular atrophy and finally cell drop-out in the central vein regions. Nine patients had fibrotic changes noted on biopsy and four had cirrhosis. Two of the four patients with cirrhosis were thought to have alcoholic liver disease and two had postnecrotic cirrhosis (one hepatitis B and one non-A non-B hepatitis).

Operative Management

Thirty portosystemic shunt procedures were performed on the 26 patients included in this study. As the initial procedure, 11 patients underwent a mesocaval shunt and 15 underwent a mesoatrial shunt. Mesocaval shunts were performed using a 16-mm or 18-mm knitted Dacron graft in a 'C-type' configuration as described previously.¹¹ The first seven mesoatrial shunts used a 16-mm woven Dacron graft. The prosthesis was anastomosed first to the superior mesenteric vein in end-to-side fashion and then passed through the transverse mesocolon into the lesser sac. The graft then passed anteriorly through the greater omentum, and anterior to the stomach and left lobe of the liver, into the anterior mediastinum, and exited into the right chest. The atrial anastomosis was performed end-to-side through an anterior right thoracotomy. Concern that graft compression at the level of the sternum might result in reduced long-term patency was realized when reoperation for focal high-grade stenosis was required in a young woman 10 months after mesoatrial shunt. Since that time

TABLE 2. *Etiologic Factors in 26 Patients with the Budd-Chiari Syndrome*

Factor	Mesocaval Shunt	Mesoatrial Shunt	Both
Polycythemia	4 (36%)	5 (33%)	9 (35%)
Estrogen use	3 (27%)	3 (20%)	6 (23%)
Previous hepatitis	2 (18%)	3 (20%)	5 (19%)
Cirrhosis	1 (9%)	3 (20%)	4 (15%)
Hepatic malignancy	0	1 (7%)	1 (4%)
Paroxysmal nocturnal hemoglobinuria	1 (9%)	0	1 (4%)
ITP	0	1 (7%)	1 (4%)
Idiopathic	2 (18%)	3 (20%)	5 (19%)

ITP, idiopathic thrombocytopenic purpura

and for the remaining eight patients, a modified 16-mm woven Dacron or ring-reinforced Gortex prosthesis, externally supported with an 8-cm silicone rubber cuff has been used.¹² The silicone cuff is positioned beneath the sternum as the graft traverses the diaphragm into the anterior mediastinum.

The decision as to which shunt to select was largely based on radiographic information. All four patients demonstrating total inferior vena cava occlusion were managed with a mesoatrial shunt. The nine patients without evidence of caval obstruction were treated with mesocaval shunts. If significant but not total vena caval obstruction was noted, as was the case in 13 patients, a mesoatrial shunt was the initial procedure for 11 patients and a mesocaval shunt was performed in 2 patients. One of these two patients who underwent a mesocaval shunt, despite a narrowed intrahepatic vena cava and caval gradient of 16 mmHg, required conversion to a mesoatrial shunt 2 weeks later. Two patients who underwent mesoatrial shunt as the initial surgical procedure required shunt revision at 6 months and 11 months after operation. In one instance a second revision was performed 5 years after operation.

Clinical Course

Eight of the twenty-six patients (31%) died before discharge from the hospital. The four patients who died within 30 days of their surgery were among the earliest treated at Johns Hopkins (before 1984). The first patient in the Johns Hopkins series was moribund at the time her mesoatrial shunt was performed and never awakened from her encephalopathic coma. The second death occurred in a woman who at autopsy was found to have metastatic bronchogenic carcinoma. The remaining two early perioperative deaths occurred in debilitated individuals with systemic fungal or bacterial sepsis before operation. Of the four deaths that occurred after the first 30

TABLE 5. Follow-up of 8 Patients with the Budd-Chiari Syndrome Discharged Alive and Well After Mesocaval Shunt

Patient	Status	Months After Operation	Cause of Death
1	A & W	150	—
2	A & W	132	—
3	Died	84	Unknown
4	A & W	46	—
5	A & W	37	—
6	A & W	24	—
7	A & W	6	—
8	A & W	2	—

—, still alive at time of publication.

postoperative days, but before discharge, three were in women older than 64 years. The remaining patient, who was noted before operation to have significant vena caval compression, thrombosed her mesocaval shunt 2 weeks after operation, underwent revision to a mesoatrial shunt, and died 1 month later. Autopsy consent was obtained for five of the eight hospital deaths. In all five patients the portosystemic graft was determined to be patent at the time of death. Of the seven patients who have undergone portosystemic decompression for the Budd-Chiari syndrome since 1986, six were discharged from the hospital alive and well with patent shunts.

Eighteen of the twenty-six patients were discharged alive and well with patent shunts. This included 8 of the 11 patients (73%) who underwent a mesocaval shunt and 10 of the 15 patients (66%) who underwent a mesoatrial shunt. Shunt patency was documented by angiography or more recently by computed tomography.¹³ Median follow-up for the 18 survivors was 43 months (range, 9 months to 13 years). There were five late deaths, four in the mesoatrial group and one in the mesocaval group. Liver failure was responsible for three of these deaths, a bleeding duodenal ulcer for one, and in one case the cause of death was unknown. Two of the five late deaths occurred in patients with cirrhosis or evidence of pre-existing infectious hepatitis before their shunt procedure (Tables 4 and 5). Actuarial survival statistics for all Budd-Chiari patients treated surgically at The Johns Hopkins Hospital stratified by type of shunt performed is shown in Figure 1. The 3- and 5-year survival rates for all patients in the study were 65% and 59%, respectively. Patients who underwent a mesoatrial shunt had 3- and 5-year survival rates of 60% and 49%, respectively. The 5-year actuarial survival rate for the mesocaval group was 73%, with no deaths from time of discharge to the 5-year mark. One patient treated with a mesocaval shunt died of unknown causes 80 months after his surgery.

Over the past 4 years 10 patients with the Budd-Chiari syndrome have undergone mesoatrial (5 patients) or mesocaval (5 patients) shunts. Eight of these ten patients are

TABLE 4. Follow-up of 10 Patients with the Budd-Chiari Syndrome Discharged Alive and Well After Mesoatrial Shunt

Patient	Status	Months After Operation	Cause of Death
1	A & W	80	—
2	Died	75	Liver failure
3	Died	60	Bleeding duodenal ulcer
4	A & W	58	—
5	Died	40	Liver failure
6	A & W	36	—
7	A & W	29	—
8	Died	5	Liver failure
9	A & W	3	—
10	A & W	2	—

A & W, alive and well.

—, still alive at time of publication.

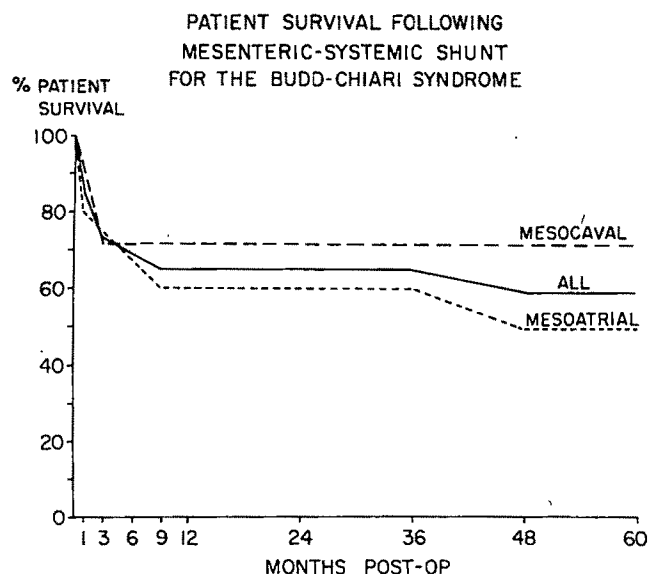


FIG. 1. Actuarial survival for patients with the Budd-Chiari syndrome treated by either mesocaval or mesoatrial shunt.

alive and well with patent shunts. Mean follow-up for this group of recently treated patients is 27 months (range, 9 to 49 months).

Recurrent ascites occurred in 6 of the 18 long-term survivors. Graft thrombosis was documented in four of these patients (three mesoatrial and one mesocaval). In the face of graft occlusion the ascites were managed by LeVein shunt (two patients), redo mesoatrial shunt (one patient), or retrohepatic cavoplasty (one patient).¹⁴ Two patients who underwent mesocaval shunt developed shunt stenosis at the venocaval anastomosis. They were successfully treated by transluminal angioplasty with resolution of the recurrent ascites. One patient with established cirrhosis at the time of mesoatrial shunt subsequently developed a hepatoma and underwent a successful orthotopic liver transplant.¹⁵

Discussion

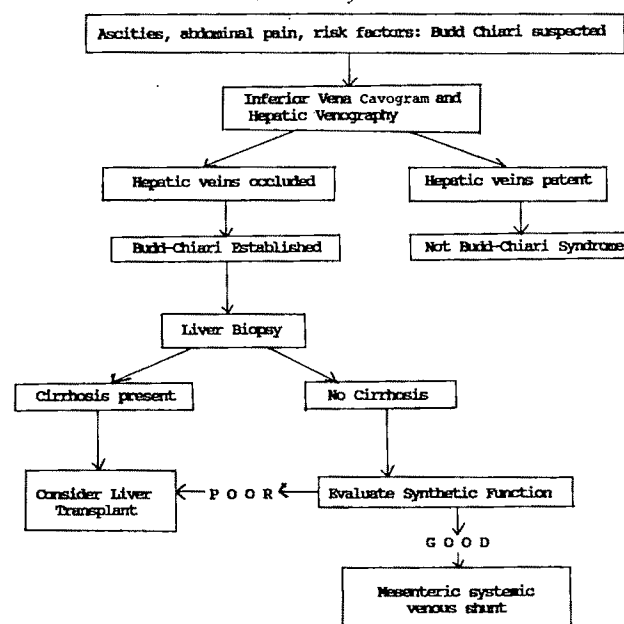
Untreated hepatic venous thrombosis results in progressive liver failure and ultimately death. There are sporadic reports of spontaneous resolution and recovery, but the natural history of this condition and the associated high rate of death is well documented.¹⁶ Medical therapy alone has little impact on the progression of the Budd-Chiari syndrome. In a study reported by McCarthy et al.¹⁷ 12 of 14 patients with the Budd-Chiari syndrome who were managed nonsurgically died within 6 months of diagnosis.

Table 6 provides an algorithm for the diagnosis and treatment of the Budd-Chiari syndrome. The development of ascites with or without abdominal pain should alert one to the possible diagnosis of this disorder. The

presence of polycythemia, estrogen usage, previous hepatitis, or cirrhosis should heighten one's suspicion. However 19% (5 of 26) of the patients with this syndrome had no identifiable predisposing factors in our series. Altered liver function is not pronounced in the early stages of the Budd-Chiari syndrome and evaluation of serum chemistries adds little to the establishment of the diagnosis. Mild elevations of the prothrombin time and serum bilirubin may be observed, but in many patients these tests, along with the serum transaminases, are normal. Serum albumin levels may be low, reflecting both protein loss into the ascites and decreased synthesis. Hepatic venography and inferior venacavography are effective in definitively establishing the diagnosis of the Budd-Chiari syndrome. The hepatic veins may be completely occluded but frequently are visualized with the 'spider web' pattern resulting from partial recanalization.

A percutaneous liver biopsy is very useful in deciding whether one should recommend mesenteric-systemic venous decompression for these individuals. The presence of massive ascites and coagulopathy has been thought to be a contraindication to liver biopsy. In this series no morbidity or mortality resulted from routine percutaneous liver biopsies and we would suggest that the results of this procedure can significantly alter the form of surgical therapy recommended. Orthotopic liver transplantation is now an accepted surgical procedure for the treatment of end-stage liver disease and several transplant centers have advocated transplantation as the definitive therapy for the Budd-Chiari syndrome.¹⁸ A multicenter analysis of patients with the Budd-Chiari syndrome treated by liver

TABLE 6. *Diagnosis and Treatment of Suspected Budd-Chiari Syndrome*

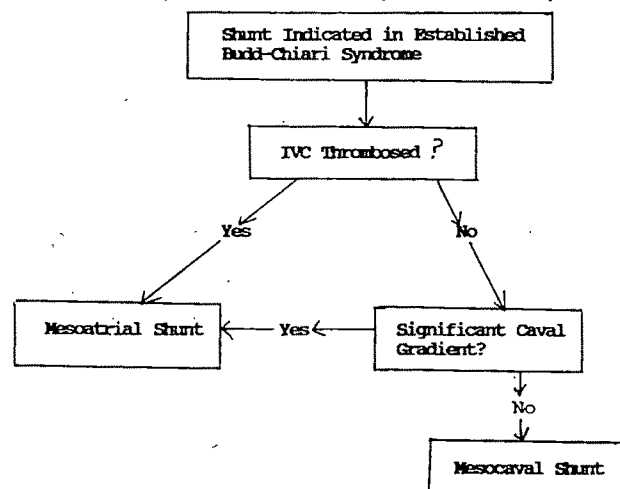


transplantation indicate a 3-year survival rate of 54%.¹⁰ We would suggest using the liver biopsy results to determine whether a patient will benefit most from a shunt or a liver transplant. Histologically hepatic vein occlusion produces a pattern of intense centrilobular congestion. With continued obstruction to venous drainage, the hepatocytes atrophy and cell regeneration is impaired.¹⁹ We have shown previously that following successful surgical decompression the resolution of this pathologic picture can be dramatic.¹⁹ Liver biopsies taken several months after successful mesenteric-systemic venous shunting appear essentially normal. Sometimes, however, the liver histopathology has a significant component of cirrhosis that may be due to either protracted passive congestion of the liver secondary to hepatic vein occlusion or a pre-existing illness. Laennec's cirrhosis or postnecrotic cirrhosis was identified in 15% (4) of the patients in this series. We think these patients with the Budd-Chiari syndrome with cirrhosis are best managed by orthotopic liver transplantation.

If it is decided that a portosystemic shunt is the appropriate therapy, the type of shunt must be chosen. Understanding the pathophysiology of the Budd-Chiari syndrome has allowed us to refine the surgical treatment of this illness and suggest guidelines for shunt selection. Typically the liver in patients with the Budd-Chiari syndrome appears swollen and edematous with blunted edges. The caudate lobe, which drains directly into the inferior vena cava *via* several short veins, often hypertrophies in response to the dysfunctional state of the remaining part of the organ. Frequently the caudate lobe hypertrophy produces compression of the inferior vena cava. Others have suggested that hypertrophy of the right hepatic lobe or possibly a process of pericaval fibrosis also may lead to retrohepatic caval obstruction.⁵ Regardless of etiology, thrombosis or severe occlusion of the retrohepatic vena cava has technical implications for selecting the most appropriate type of portosystemic decompression. Table 7 outlines the decision tree used at the Johns Hopkins Hospital. For those patients with an established diagnosis of the Budd-Chiari syndrome who are thought to be appropriate candidates for a shunt procedure, inferior vena cavography is most useful in selecting the surgical procedure. Patients with inferior vena caval thrombosis or with significant caval occlusion (compression producing a gradient more than 20 mmHg or a reduction in intraluminal diameter more than 75%) should undergo a mesoatrial shunt. Those patients without significant vena caval obstruction can be managed effectively with a mesocaval shunt.

Selection of the mesoatrial shunt for the Budd-Chiari syndrome patients with inferior vena caval compression is not a uniformly supported concept. Vons et al.²⁰ performed seven mesocaval shunts in patients with the Budd-

TABLE 7. Portosystemic Shunt Selection for Budd-Chiari Syndrome



Chiari syndrome who had a mean caval pressure of 15 mm of mercury. Because there were no graft thromboses in their series, they concluded that compression of the inferior vena cava should not persuade the surgeon to abandon a mesocaval or portacaval shunt in favor of a mesoatrial procedure. Based on the success of Vons and others using the mesocaval or portocaval shunts despite high caval pressures, two such patients underwent mesocaval grafting at Johns Hopkins. In one case the shunt thrombosed at 2 weeks and required conversion to a mesoatrial shunt. The second patient developed shunt stenosis at the vena caval anastomosis possibly due to continued retrohepatic caval compression and a low flow state and required balloon dilatation at 6 months. Information regarding the pressure gradient across the region of caval narrowing, the crucial factor in selecting a shunt, was not included in the study by Vons et al.²⁰ With the caval pressure stated in the article, the gradient could not have been as high as the 20 mm of mercury level, above which we would now favor a mesoatrial shunt.

The perception that mesoatrial shunts are highly susceptible to thrombosis has led to a reluctance among some individuals to use this procedure. Others who have used the mesoatrial shunt have felt obliged to convert the original mesoatrial shunt to a mesocaval shunt once the hepatic congestion, and presumably caval compression, has resolved. Recently Wang et al.²¹ reported 100 patients with the Budd-Chiari syndrome, 81 of whom were treated surgically in Beijing, China. Although these patients will need more extensive follow-up (range in study, 2 to 66 months) to accurately assess their outcome, 84% were alive at the time the manuscript was written. This included 22 of the 25 patients treated by mesoatrial shunt. Successful use of the mesoatrial shunt for five patients with the Budd-Chiari syndrome and concomitant vena caval occlusion or obstruction has been reported recently by Williams et

al.²² All patients recovered and were discharged with patent shunts. Of the 15 patients in our series who underwent a mesoatrial shunt, only one developed graft thrombosis acutely. Three of the ten patients with mesoatrial shunts who were discharged alive and well from the hospital developed graft thrombosis at 2 months, 6 months, and 4 years. The last two of these patients underwent redo mesoatrial grafts using the silicone sleeve reinforced prosthesis and both patients are alive and ascites free 6 and 3 years, respectively, after their graft revision. Thus only 1 of the 10 patients developed a graft thrombosis resulting in death. Ascites is such a constant clinical component of the Budd-Chiari syndrome (more than 90%) it is unlikely that postoperative patients who remain healthy and ascites free will suffer an unrecognized graft thrombosis. We would suggest that elective conversion of a mesoatrial to a mesocaval shunt offers no clear benefit to the patient. If thrombosis does occur in the mesoatrial shunt, revision is usually successful.

In the Johns Hopkins series side-to-side portacaval shunt has not been used as a therapeutic option in the treatment of the Budd-Chiari syndrome for two reasons. The hypertrophied caudate lobe present in these patients often renders this procedure technically difficult. Furthermore, should liver transplantation be required in the future (due to shunt failure, cirrhosis, tumor, and so on), the presence of a side-to-side portacaval shunt increases the transplant mortality rate dramatically.²³ Mesocaval grafts are performed away from the porta hepatis, which then does not become a reoperative field at the time of liver transplantation. Unlike portacaval shunts, mesocaval shunts require only simple ligation at the conclusion of the transplant operation.

Although a cumulative 5-year patient survival rate of 59% with the Budd-Chiari syndrome is certainly an improvement over their predicted survival rate with medical therapy alone, the 80% long-term survival rate noted in the recently treated patients in our series is even more encouraging. Certainly a number of deaths among those patients treated early in our experience can be attributed to the moribund condition of patients selected for a procedure, which, at that time, was considered experimental. Furthermore refinements of the operative technique and graft material have decreased the risk of shunt failure. The appropriate selection of mesocaval shunt, mesoatrial shunt, or orthotopic liver transplantation should result in the safe and successful surgical management of most patients with the Budd-Chiari syndrome.

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Clinicopathologic Comparisons Between Estrogen Receptor-positive and -negative Hepatocellular Carcinomas

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During the past 8 years, estrogen receptors (ERs) in the cytosol of hepatocellular carcinoma (HCC) were assayed in 66 unselected patients without preceding treatments on whom radical hepatic resection was performed. Twenty-six patients had ERs of 0.9 to 13.4 fmol/mg protein with a mean dissociation constant of 7.8×10^{-10} M. The remaining 40 patients had no detectable amount of the receptor. There were no substantial differences between the ER-positive and ER-negative groups in preoperative clinical and laboratory data such as sex, age, alcohol abuse, underlying liver disease, and hepatic functions. Large tumors were more common in the ER-negative group and therefore the incidence of major hepatic resection was significantly higher in this group. Histopathologic studies revealed no substantial differences between the two groups. Operative mortality rate was 11.5% in the ER-positive and 12.5% in the ER-negative group. Excluding eight operative deaths, the rate and time of tumor recurrence in the residual liver and long-term survival rate were identical for the two study groups. The current results may indicate that the presence or absence of ERs in human HCC does not correlate to either biologic or pathologic characteristics of this tumor, but the true role of ERs in human HCC remains to be elucidated.

THE EFFECT OF sex hormones on the liver has been studied in the past decade and it is generally accepted that the liver is one of the target organs for estrogens. Since the first description by Baum and associates¹ in 1973, a possible correlation of estrogens with the development of hepatic tumors has been suggested by many reports of oral contraceptive-associated liver cell adenoma or carcinoma. Withdrawal of contraceptive pills sometimes induces regression of the drug-induced hepatic tumors,²⁻⁴ which may suggest that the effect of estrogens on the liver is mediated by the hormone receptors.^{5,6}

Most hepatocellular carcinoma (HCC) in Japan occur in men and is associated with underlying cirrhosis of the liver. Male patients with cirrhosis, particularly alcoholic

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patients, are known to have elevated estrogen and decreased testosterone concentrations in the blood.^{7,8} We have also found that the estrone (E_1) to testosterone ratio is significantly raised in male patients with both HCC and liver cirrhosis, compared with those with cirrhosis only.⁹ For these reasons we have estimated estrogen receptor (ER) in HCC and the surrounding liver using fresh surgical specimens and elucidated that ERs are present in 38% of male and 37% of female patients with HCC.^{10,11}

The aim of this study was to retrospectively evaluate the clinicopathologic differences between ER-positive and ER-negative HCCs.

Materials and Methods

During the past 8 years, ERs were assayed for primary HCC in 66 patients on whom radical hepatic resection was performed. No patients had previous treatments such as chemotherapy, radiotherapy, or embolization of the hepatic artery before current liver resection was performed. Estrogen receptors in the tumor were detected in 26 patients but not in the remaining 40. Detailed clinicopathologic comparisons were undertaken among those patients with ER-positive and ER-negative HCCs. The mean follow-up times were 43.3 ± 29.5 months in the ER-positive group and 47.3 ± 24.8 months in the ER-negative group.

Serum α -fetoprotein and hepatitis B markers were assayed by radioimmunoassay methods. The diagnosis of HCC and underlying liver disease was performed histologically in all patients. Estrogen receptor-positive HCCs were found more frequently in men than in women, but

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the difference was not significant. There were no significant differences between the two groups in age distribution and underlying liver disease. Alcohol abuse was noted in 25 patients but no substantial difference was observed between the ER-positive and ER-negative groups (Table 1). Table 2 shows the results of preoperative laboratory tests. There were no substantial differences between the two study groups. Due to a high incidence of associated liver cirrhosis, atypical minor hepatic resections were performed in most patients (Table 3). One or two segmentectomy in this study was defined according to the description by Couinaud.¹² Major hepatic resections, which were resections equal to or larger than left lobectomy, were performed on nine patients in the ER-negative group but none in the ER-positive group ($p < 0.01$). This could be attributed to the fact that large tumors were more common in the former group than in the latter, although the difference was not significant (Table 4). The incidence and contents of postoperative chemotherapy were similar in both groups (Table 3).

Postoperative Work-up

All patients, except for those who died shortly after operation, were evaluated with computed tomography, ultrasonography, and, if necessary, selective angiography just before discharge from the hospital. They were all proved to have no residual tumors in the liver and no distant metastases. After discharge from the hospital, the patients were followed at 2-week intervals during the first 6 months and monthly thereafter. Imaging studies were repeated every 3 months. When tumor recurrence was

TABLE 2. Laboratory Data in Patients with ER-positive and -negative Hepatocellular Carcinomas

Data	ER (+) (n = 26)	ER (-) (n = 40)
AST (IU/mL)*	91 ± 50	86 ± 48
ALT (IU/mL)†	85 ± 64	78 ± 45
LDH (IU/mL)	328 ± 82	340 ± 115
Bilirubin (mg/100 mL)	0.9 ± 0.7	0.9 ± 0.5
Albumin (g/100 mL)	3.7 ± 0.5	3.8 ± 0.5
Cholesterol (mg/100 mL)	142 ± 27	147 ± 29
BSP R30‡	30.0 ± 13.3	24.7 ± 11.7
ICG R15§	25.2 ± 14.1	21.1 ± 11.4
Serum AFP (ng/mL)		
Less than 20	5	12
21-400	15	18
401-10,000	4	8
More than 10,000	2	2
Hepatitis B virus		
HBs-antigen (+)	4	9
Anti-HBs (+)	5	18
Anti-HBc (+)	20	26
All negative	6	10

* Aspartate aminotransferase (normal, 0 to 37).

† Alanine aminotransferase (normal, 3 to 32).

‡ Bromosulphalein retention rate at 30 minutes (normal, 0% to 10%).

§ Indocyanine green retention rate at 15 minutes (normal, 0% to 10%).

^{||} $p < 0.05$.

suspected, the patient was hospitalized for angiography. Whenever the recurrent tumor was resectable, second hepatic resection was performed. If the tumor was not resectable, chemotherapy with or without embolization of the hepatic artery was carried out.

Estrogen Receptor Assay

Specimens for analysis were obtained at the time of operation in all cases. The tumor was frozen in liquid nitrogen immediately after removal and was stored at -80°C until the receptor assays could be performed. The chemicals and the method of cytosol preparation are described elsewhere.^{10,11} Aliquots of cytosol (0.15 mL) were incubated with increasing concentrations of ³H-E₂ (0.125

TABLE 1. Clinical Data in Patients with ER-positive and -negative Hepatocellular Carcinomas

Data	ER (+) (n = 26)	ER (-) (n = 40)
M/F	23/3	29/11
Age (years)	59.3 ± 7.7	58.1 ± 10.3
Duration of liver disease (years)		
5 or less	10	18
6-10	5	7
11-20	7	13
More than 20	4	2
Alcohol abuse*		
No	17	24
Yes	9	16
Liver disease		
Chronic hepatitis	5	11
Liver cirrhosis	21	29
Child's class		
A	13	29
B	10	10
C	3	1

* Those who consumed more than 50 g of alcohol every day for more than 5 years.

TABLE 3. Operative Methods and Postoperative Chemotherapy in Patients with ER-positive and -negative Hepatocellular Carcinomas

Data	ER (+) (n = 26)	ER (-) (n = 40)
Liver resection		
Wedge resection	13	16
One segmentectomy	8	12
Two segmentectomy	3	1
Left lateral segmentectomy	2	2
Left lobectomy	0	2
Right lobectomy	0	6
Extended right lobectomy	0	1
Postoperative chemotherapy		
No	18	28
Yes	8	12

TABLE 4. *Histopathologic Data of ER-positive and -negative Hepatocellular Carcinomas*

Data	ER (+) (n = 26)	ER (-) (n = 40)
Tumor size (cm)		
2 or less	3	6
2.1 to 5.0	18	21
5.1 to 10.0	5	11
Larger than 10	0	2
Capsule		
Absent	3	6
Present	23	34
Daughter nodule		
Absent	21	23
Present	5	17
Histologic type		
Trabecular	17	32
Trabecular + pseudoglandular	2	4
Trabecular + compact	2	2
Trabecular + clear cell	1	0
Compact	2	1
Compact + pseudoglandular	2	1
Differentiation grade		
I	1	0
II	9	14
III	5	7
I + II	1	4
II + III	9	15
II + III + IV	1	0

to 2.0 nmol/L [nanomolar]) in the presence or absence, in an excess of 500 times of unlabeled E_2 for 16 to 18 hours. After the incubation a μ L dextran-coated solution (2.5% activated charcoal Norit A, 0.025% dextran T-40 in TEGT buffer; 10 mL TRIS-HCl, 1.5 mmol/L [millimolar] EDTA, 30% (u/v) glycerol, and 1 mmol/L thio-glycerol) was added to the tubes, which were incubated for 20 minutes and then centrifuged for 15 minutes at 1500g. The radioactivity in the supernatant was measured by liquid scintillation counting. The data were analyzed by the method of Scatchard,¹³ which follows subtraction of nonspecific estrogen binding.

Statistical Methods

Statistical comparisons for significance were made using unpaired Student's t test and the chi square test with a single degree of freedom; p values less than 0.05 were considered statistically significant. Cumulative survival rates were calculated using the Kaplan-Meier method.

Results

Estrogen Receptor

Estrogen receptors were detected in the cytosol of HCCs removed from 26 patients. The titer of ER ranged from 0.9 to 13.4 fmol/mg protein (mean $\pm$ SD, 4.6 ± 3.6 fmol/mgp) with the dissociation constants ranging from 1.5 to

30.6×10^{-10} M (mean $\pm$ SD, $7.8 \pm 7.7 \times 10^{-10}$ M). There were no detectable amounts of ERs in the tumors taken from the remaining 40 patients.

Operative Morbidity and Mortality

Among 26 patients with ER-positive HCCs, three died after operation. Two patients died of liver failure on the 29th and 34th postoperative days, respectively. The third patient died of brain stem hemorrhage 5 days after left lateral segmentectomy. On the other hand, four patients in the ER-negative group died of hepatic failure 7, 11, 65, and 86 days after liver resection. Another patient in this group died of pneumonia followed by multiple-organ failure on the 117th postoperative day without discharge from the hospital. The operative mortality rate was 11.5% in the former group and 12.5% in the latter.

Histopathology of Hepatocellular Carcinoma

Histopathologic results of the resected HCCs in both groups are summarized in Table 4. The ER-negative group had larger tumors more frequently, but the difference was not significant. The incidence of connective tissue capsule around the tumor was similar between the groups. Daughter nodules around the main tumor were more frequently found in ER-negative patients, but the difference was not statistically significant. Also there were no differences in histologic type and differentiation grade¹⁴ of the tumors between the two study groups.

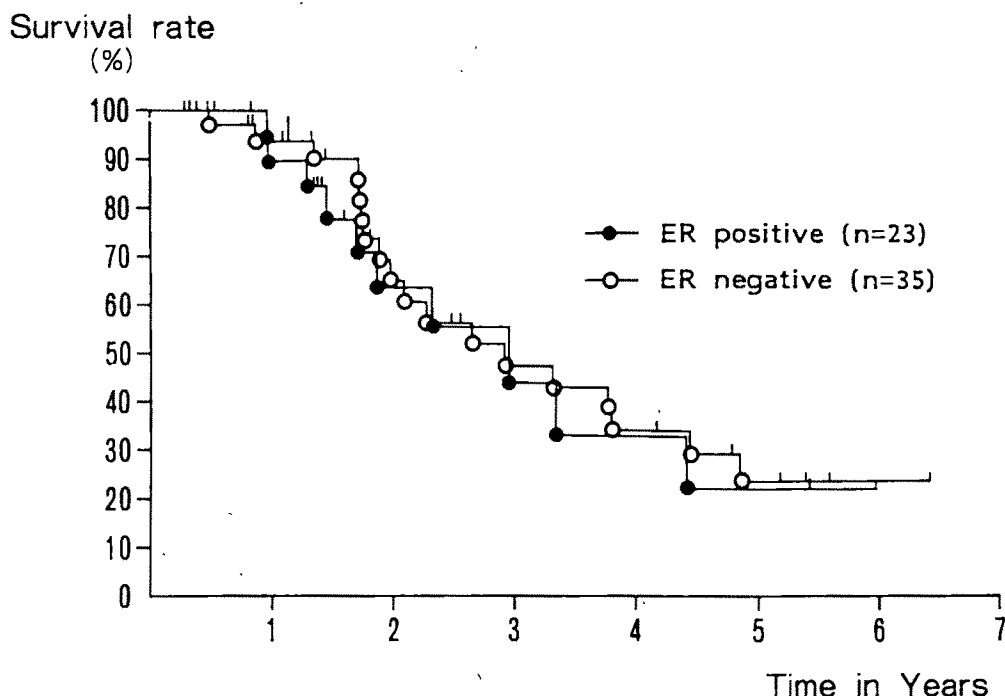
Tumor Recurrence

Excluding 8 patients who could not be discharged from the hospital, 12 (52.2%) of 23 patients in the ER-positive group and 18 (51.4%) of 35 patients in the ER-negative group had tumor recurrence in the liver up to now. The time until recurrence ranged from 4 to 43 months (mean $\pm$ SD, 18.2 ± 12.8 months) in the former group and from 3 to 40 months (mean $\pm$ SD, 16.9 ± 12.8 months) in the latter group. Thus the recurrence pattern was very similar between the two groups.

Long-term Survival

Cumulative survival curves for both patient groups are shown in Figure 1. To discover whether the presence or absence of ERs in HCC influences the survival rate, the operative deaths were excluded from the analysis. The 1- to 6-year survival rates in the ER-positive and ER-negative groups were 89.5% and 93.7%, 55.7% and 60.5%, 33.4% and 43.2%, 22.3% and 34.6%, 22.3% and 23.7%, and 22.3% and 23.7%, respectively. There was no significant difference between the two groups throughout the observation.

FIG. 1. Cumulative survival curves in patients with ER-positive HCCs and those with ER-negative tumors after radical hepatic resection. Operative deaths were excluded. There was no significant difference between the two groups.



Discussion

In the current study, we have retrospectively evaluated the characteristics of ER-positive and ER-negative HCCs in terms of various clinicopathologic parameters. No substantial differences were found in preoperative clinical and laboratory data between the two comparative groups of patients. The ER-negative group tended to have larger tumors and therefore the incidence of major hepatic resection was higher in this group. No significant differences could be observed in detailed histopathologic data between the ER-positive and ER-negative groups. The operative morbidity and mortality rates were also similar in both groups. Excluding operative and in-hospital deaths, the rate and pattern of tumor recurrence in the liver and long-term survival rate were identical in both groups.

Previously we reported that androgen receptors (AR) exist in 74% of male and 37% of female HCC patients^{11,15} and that the presence of AR is strongly related to the high recurrence rate in the residual liver and low long-term survival rate.¹⁶ With those laboratory and clinical results, we have suggested a hypothesis that HCC is principally androgen dependent. Estrogen receptors, on the other hand, do not seem to characterize this tumor as shown in this study. Thus the presence or absence of ERs in HCC can not be a prognostic factor after radical resection of HCC. Then what is the genuine role of ERs present in HCC?

Although most carcinogens can be mutagenic *in vitro*, this has not been demonstrated for estrogens.¹⁷ Reznik-Schuller¹⁸ found the development of liver tumors (he-

pato cellular adenoma, carcinoma, and cholangiocarcinoma) in 29% of male European hamsters treated with diethylstilbestrol (DES). This is the first report showing that estrogens alone are carcinogenic. Other authors have suggested that estrogens promote the effect of carcinogens.¹⁹⁻²¹ Sumi et al.²² initially found a synergistic effect of DES and carcinogens on the development of liver tumors in male Wistar/Furth rats. Later they found that DES itself has a direct carcinogenic effect on the liver and that this effect is not mediated by prolactin.²³ In 1980 Higashi et al.²⁴ reported that oral administration of synthetic estrogen and progestogen could induce HCC in female Wistar rats.

Theoretically it is assumed that the tumorigenic effect of estrogens may be through ERs. Li and Li²⁵ suggested a possibly important role of ERs in the tumorigenic process because a higher value of both cytosolic and nuclear ERs in hamster livers was observed when the regimen of DES and α -naphthoflavon was made more tumorigenic. The presence of ERs in the human liver was first found by Duffy and Duffy⁵ in 1978. Friedman et al.⁶ estimated ERs in human HCCs. The titer of ER in HCC taken from five male adults ranged from 0.9 to 6.4 fmol/mg cytosolic protein. Other groups,²⁶ including our own,^{10,11} found similar results.

Despite those experimental and clinical investigations, it is not well known whether the presence of ER is related to the development of HCC in humans. Also it must be elucidated why some HCCs are ER positive and others are not. However, as far as the current study is concerned, the presence of ERs in HCC does not influence biologic

characteristics of this tumor in humans, which is a significant contrast to that of AR-positive and AR-negative HCCs.¹⁶

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Pathogenicity of the Enterococcus in Surgical Infections

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The enterococcus has been relegated to a position of unimportance in the pathogenesis of surgical infections. However the increasing prevalence and virulence of these bacteria prompt reconsideration of this view, particularly because the surgical patient has become increasingly vulnerable to infectious morbidity due to debility, immunosuppression, and therapy with increasingly potent antibiotics. The enterococcus is a versatile opportunistic nosocomial pathogen, causing such diverse infections as wound, intra-abdominal, and urinary tract infections; catheter-associated infection; suppurative thrombophlebitis; endocarditis; and pneumonia. Although surgical drainage remains the cornerstone of therapy for enterococcal infections involving a discrete focus, in the circumstances typified by the compromised surgical patient, specific antibacterial therapy directed against the enterococcus is warranted. Recent evidence indicates that parenteral antibiotic therapy for enterococcal bacteremia is mandatory and that appropriate therapy clearly reduces the number of deaths.

THE PATHOGENIC ROLE of enterococci in surgical infections has long been debated. The prevailing wisdom has been to discount the importance of enterococci in the pathogenesis of these infections. However these bacteria are increasingly prevalent in nosocomial infections arising from many sources, including surgical wounds and intra-abdominal abscesses, leading to reconsideration of the virulence of these organisms. The probable reasons for the increased frequency of the enterococci in nosocomial infections are many. These reasons include increasingly ill hospital inpatients, the increased need for invasive monitoring and therapy for these seriously ill patients, and the increasing use of extremely potent broad-spectrum antibiotics. Furthermore increasing numbers of immunosuppressed patients, such as organ transplant recipients, patients with active autoimmune

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diseases requiring glucocorticoid therapy, and HIV-infected patients also require surgical therapy. There is also evidence that the enterococci are versatile in their development of new mechanisms of resistance to antimicrobial agents.

There is renewed debate regarding the need to use antibiotic therapy active against enterococci in patients with intra-abdominal and other surgical infections. Whether the immunosuppressed patient or the patient previously treated with broad-spectrum antibiotics represents a special circumstance with respect to prophylaxis or empiric therapy for presumed enterococcal infection is also at issue.

Clinical and Experimental Observations

The incidence of enterococcal infections is clearly increasing.¹⁻⁵ Enterococci account for more than 9% of isolates from nosocomial infections,⁶ making these organisms collectively the third most commonly encountered nosocomial isolate.⁷ The overall incidence of isolation of enterococci from blood cultures is also increasing, and currently is about 5%.^{8,9} However enterococci have been reported in 8.4% of positive blood cultures taken because of a suspected infection from a series of general and thoracic surgical patients.¹⁰ A large series of enterococcal bacteremias complicating burn wound sepsis also has been reported.⁵ A longitudinal study of enterococcal bacteremia in the University of Wisconsin Hospitals showed a striking

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annual increase in the number of enterococcal bacteremias beginning in 1975.⁴ Forty-eight per cent (74 of 153) of those patients had undergone recent surgery or sustained major burns or multiple injuries. Four enterococcal species can cause human disease. *Enterococcus faecalis* accounts for 85% to 90% of isolates, *E. faecium* accounts for 5% to 15% of strains, while *E. durans* and *E. casseliflavus* are rarely identified clinically.¹ The genus *Enterococcus* has recently gained formal taxonomic status based on DNA homology.¹¹

Enterococci traditionally have been considered non-pathogenic other than in their well-recognized role as causative agents in urinary and biliary tract infections. There has been reluctance to consider them pathogenic elsewhere, even if isolated in pure culture. Enterococci isolated in pure culture from surgical wounds are rarely associated with signs of wound infection such as fever, wound erythema or tenderness, or leukocytosis.¹² Experimental inoculation of enterococci into the peritoneal cavity of rats did not cause death from sepsis or subsequent abscess formation,¹³ although a synergistic relationship between enterococci and anaerobic gram-negative bacilli for the production of abscesses was identified.^{14,15} Although enterococci in pure culture are sometimes associated with infection outside the biliary or urinary tract,¹⁴ most surgical infections are mixed infections. Virulence has generally been attributed either to aerobic gram-negative or to anaerobic flora when enterococci have been isolated with other bacteria.

There is ample experimental^{16,17} and clinical evidence that mixed intra-abdominal infections that contain enterococci can be treated successfully with appropriate surgical drainage and an antibiotic regimen that is not active against enterococci.^{16,18,19} Furthermore enterococcal bacteremia has been considered rare as a consequence of surgical infection,^{12,20} even in the absence of specific anti-enterococcal therapy. The partial efficacy of gentamicin, commonly used in intra-abdominal sepsis, against the enterococcus may explain this observation.²¹ In addition results of treatment of pure enterococcal infections have been variable, prompting questions about the pathogenicity of enterococcal infestations.¹⁰

The historical disregard for the pathogenicity of the enterococcus also requires re-examination because the nosocomial nature of these infections is increasingly clear.^{4,22-26} Maki and Agger⁴ considered 77% of their 153 cases to be nosocomial in origin. Furthermore the 37 nosocomial intra-abdominal or surgical wound infections constituted the largest patient subgroup reported with enterococcal bacteremia in that series, suggesting that surgical patients may be at particular risk. An indwelling urinary catheter, one or more intravascular catheters, or both were present in all but one of these cases. Twenty-four of the cases consisted of catheter-associated entero-

coccal bacteremia.⁴ There are many other reports of enterococcal infection related to indwelling urinary or vascular catheters as well. Enterococci represent about 15% of all urinary tract isolates.^{22,27} Enterococcal bacteriuria is strongly associated with manipulation of the urinary tract²² and with previous antibiotic therapy,^{28,29} and clearly can lead to bacteremia.³⁰ Enterococcal contamination of intravascular devices is less common but clearly occurs.^{26,31,32} This can lead not only to bacteremia from contaminated central venous catheters^{31,32} but also to the dangerous complication of suppurative thrombophlebitis.²⁶

The association between enterococcal infection and previous antibiotic therapy has been made at sites other than the urinary tract. For example enterococcal pneumonia has been reported after cefamandole therapy in patients also receiving enteral hyperalimentation through a nasoenteric tube.³³ Enterococci are resistant to most antibiotics, including most beta-lactam antibiotics.³⁴ Even antibiotics with activity against enterococci (such as ampicillin and vancomycin) are not bactericidal against most strains.^{35,36} Combinations of these agents with an aminoglycoside (usually gentamicin) may produce a synergistic effect when aminoglycoside penetration is promoted by damage to the bacterial cell wall by the other antibiotic in combination,³⁷ although the clinical benefit of *in vitro* antibacterial synergy is difficult to quantitate. The increase in enterococcal urinary tract infections in the past 10 years has paralleled the striking increase in the use of cephalosporin antibiotics during that period,²⁹ and a similar pattern is emerging for intra-abdominal infections.²¹ None of the currently available cephalosporin antibiotics are therapeutically beneficial against enterococci.^{36,38-40} Many reports of secondary enterococcal infection after treatment of intra-abdominal infections with these agents have also appeared,⁴¹⁻⁴³ particularly as a cause of treatment failure after therapy with moxalactam.⁴⁴⁻⁴⁹ Furthermore these infections have emerged after short-course presumptive therapy for penetrating abdominal trauma with both moxalactam and other cephalosporin agents,⁴³ in which a majority of specimens from postoperative wound and intra-abdominal infections included enterococci. Enterococcal intra-abdominal abscesses have been reported after major hepatic resection for trauma or tumor, even in the setting of appropriate (piperacillin/gentamicin) antibacterial prophylaxis.⁵⁰

Epidemiology of Enterococcal Infection

The source of the enterococci in these infections has been thought to be endogenous,²² particularly in the case of urinary tract infection. Enterococci are present in feces in concentrations of 10⁶ organisms per gram.⁵¹ They are also indigenous to the human oral cavity,⁵² gallbladder,

female genital tract and perineum,⁵³ and male and female urethra.⁵⁴ Seriously ill patients frequently have perineal fecal contamination, and there has been scant epidemiologic documentation of epidemic enterococcal infections.⁵⁵ Even if the flora are endogenous, the hospital environment may render endogenous flora more invasive. Treatment with imipenem-cilastatin resulted in enterococcal overgrowth in fecal flora.⁵⁶ Overgrowth was observed despite the fact that *E. faecalis* is sensitive to imipenem-cilastatin *in vitro*, although *E. faecium* is resistant. Bacterial overgrowth may lead to intestinal bacterial translocation. It is possible that broad-spectrum antibiotic therapy may render the already compromised host susceptible to sepsis from endogenous sources, even without catheterization or other manipulation, although the pathogenicity of the translocation phenomenon in humans is still being defined. Enterococci are capable of translocation, although not to the extent of *Escherichia coli*, for example.⁵⁷ Enterococcal translocation has been reported to be facilitated in mice treated with parenteral metronidazole.^{58,59} However the assumption that enterococci arise solely from endogenous sources also requires re-examination. Zervos and colleagues^{59,60} noted a large increase in nosocomial enterococcal surgical infections caused by highly gentamicin-resistant strains at the University of Michigan, and determined in epidemiologic studies that those strains were extrinsically acquired and had been transmitted by direct contact with medical personnel. Two outbreaks of extrinsically acquired neonatal enterococcal sepsis also have been reported recently.^{61,62}

The recent exogenously acquired epidemics of enterococcal infection were caused by strains that are highly resistant to gentamicin.^{59,60} Although the incidence of high-level streptomycin resistance increased throughout the 1960s and 1970s,^{63,64} high-level gentamicin resistance is a relatively new phenomenon. Unknown as recently as 1977 at the Massachusetts General Hospital,⁶⁵ widespread reports of high-level gentamicin resistance appeared between 1979 and 1984.⁶⁶⁻⁶⁸ These gentamicin-resistant strains are generally resistant to all other aminoglycosides by a transferable plasmid-mediated mechanism that may have been originally acquired from *Staphylococcus aureus*.⁶⁹ Beta-lactamase production by gentamicin-resistant strains of *E. faecalis* has also been described.^{70,71} Gentamicin and beta-lactamase resistance may occur in tandem because the beta-lactamase gene is present on the same plasmid as that for gentamicin resistance in staphylococci.⁶⁷ This association is of concern because of the rapid proliferation of gentamicin-resistant strains. Similar proliferation of beta-lactamase-producing enterococci may make treatment of serious enterococcal infections all the more difficult.

Even more worrisome are the recent reports of vancomycin-resistant enterococci, including both *E. faecalis*

and *E. faecium*.⁷² These highly resistant strains were isolated from blood, peritoneal fluid or collections, urine, pleural fluid, or bile from 22 critically ill patients with multiple-organ failure. Beginning 3 months before the outbreak, vancomycin and ceftazidime had been used empirically for sepsis before diagnosis, further documenting the enormous capability of the enterococci to develop resistance to commonly used antimicrobial agents. The emergence of these resistant strains may be of enormous clinical significance. Many hospitalized patients are found to have gentamicin-resistant strains when the organisms are initially isolated, and other patients will acquire these resistant strains. One third of the deaths due to enterococcal infections reported by Zervos and coworkers⁶⁰ were caused by gentamicin-resistant strains.

Recommendations for Therapy

Surgical drainage or removal of infected vascular catheters or prostheses remains the cornerstone of therapy for enterococcal infections involving discrete foci—abscesses, infected wounds or burns, or ureteral or biliary obstruction. Yet the enterococci are more likely to become pathogenic or cause bacteremia in the compromised patient. In the selected circumstances typified by many surgical patients, specific adjunctive antibacterial therapy directed against enterococci is now warranted. The sick surgical patient seems almost ideally compromised from the standpoint of the enterococcus as an opportunistic pathogen, particularly after trauma, shock, major burns, organ transplantation, or persistent sepsis. Empiric therapy for the enterococcus in intra-abdominal, nonbiliary/urinary infection in the good risk patient does not appear necessary (except possibly for patients with valvular heart disease),⁴ nor is the addition of anti-enterococcal coverage (ampicillin, piperacillin, or vancomycin) necessary if initial intraperitoneal cultures yield enterococci but the patient is doing well. However, if the patient has had enterococci cultured previously during the hospitalization or if the infection is nosocomial, particularly with previous gastrointestinal or genitourinary surgery or previous antibiotic therapy, a drug effective against enterococci should be included in the regimen for both proved and presumptive abdominal/pelvic infections, burn or surgical wound infections, urosepsis, postoperative/acalculous cholecystitis, and catheter-related infection. This is especially true in patients with valvular heart disease or a prosthetic heart valve.

Enterococcal bacteremia requires parenteral antibiotic therapy.⁴ Appropriate therapy for enterococcal bacteremia without endocarditis should use a bactericidal antibiotic such as ampicillin, an acylureido penicillin (piperacillin, mezlocillin, or azlocillin), or vancomycin for 10 to 14 days.⁴ Because enterococcal bacteremia is often polymi-

crobial, appropriate antibiotic therapy also should be directed against any additional isolates. Synergistic therapy with an aminoglycoside can also be used but may not be necessary. Although some reports suggest that antibiotic therapy did not influence the outcome of intra-abdominal sepsis caused by enterococci,⁷³ recent evidence suggests that adjunctive antibiotic therapy with appropriate agents clearly reduces mortality.^{4,41} All patients with enterococcal bacteremia must be closely monitored for signs of endocarditis.

Enterococcal endocarditis should be suspected in the presence of embolic lesions or echocardiographic findings,⁷⁴ and treated with an appropriate bactericidal combination for 4 to 6 weeks.^{4,75} Penicillin, ampicillin, or vancomycin combined with an aminoglycoside (gentamicin, or streptomycin if high-level enterococcal gentamicin resistance is identified) may be administered with dosage predicated on the serum bactericidal titer of the organism.⁷⁶ Patients with prosthetic valve endocarditis may require 6 weeks of therapy.⁷⁵ The overall cure rate for enterococcal endocarditis is approximately 75%.⁷⁶ Therapy for patients in whom an extracardiac source of enterococcal bacteremia cannot be identified remains a matter of debate. Patients with valvular heart disease should be presumed to have endocarditis and should be treated accordingly.⁴ Similar recommendations recently have been made for patients without valvular heart disease.⁴ Fortunately endocarditis rarely develops after nosocomial enterococcal bacteremia^{4,8,21,41,73} and is exceedingly unusual if the enterococcal bacteremia is polymicrobial.⁴

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Pneumatosis Intestinalis

Surgical Management and Clinical Outcome

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Pneumatosis intestinalis (PI) occurs in a wide variety of patients, some of whom require urgent surgery, while others can be observed with resolution of symptoms and radiographic findings. During 1 year, 27 patients with PI were prospectively evaluated for clinical, laboratory, and radiographic features that would be useful in predicting the need for surgery, the pathologic findings, and patient outcome. Sixteen of the twenty-seven patients underwent laparotomy, with only one negative exploration. Of the 11 patients not explored, there were two deaths in moribund patients. Seven of nine patients with jejunostomy tubes, recent gastrointestinal anastomoses, inflammatory bowel disease, lactulose therapy, or chemotherapy who did not have clinical evidence of an acute surgical abdomen or metabolic acidosis survived without surgery (two deaths unrelated to the gastrointestinal tract). Patients presenting with bowel obstruction and PI required surgery in seven of nine cases, did not have necrotic bowel, and had 11% mortality. Eight patients with ischemic bowel had a 75% mortality rate, despite surgery. Patients with PI and clinical evidence of bowel obstruction or ischemia usually require urgent surgery, while asymptomatic patients without metabolic acidosis can be safely observed.

PNEUMATOSIS INTESTINALIS (PI) is defined as the presence of gas in the bowel wall and can be classified as either primary or secondary. Primary PI radiologically and pathologically consists of cystic collections of air, usually located in the colon. It is generally a benign condition that may remain stable for years but may be complicated by obstruction or bleeding. Its etiology is unknown, but its frequent association with emphysema suggests that air may dissect through the mediastinum and retroperitoneal tissues to enter the bowel mesentery and subserosal spaces.¹ Secondary PI, on the other hand, is characterized by linear or circumferential air in any part of the gastrointestinal tract and is associated with many clinical conditions. A review of 213 cases in 1952 by Koss included a 15% incidence of primary PI

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compared to 85% of cases that were secondary to other underlying disorders.² Pneumatosis intestinalis may be associated with pneumoperitoneum either as a benign condition or following perforation of a viscus. In addition PI may be associated with portal venous gas, which is often an ominous sign and has a reported mortality rate of 75%.^{3,4}

The first pathologic description of PI is attributed to DuVernoi in 1730 during a cadaver dissection.⁵ In the 18th century John Hunter contributed two specimens of hog intestine to the Museum of the Royal College of Surgeons that demonstrated multiple gas-filled cysts beneath the serosal layer.⁶ Bang⁷ in 1876 published the first comprehensive description of PI in a human, including microscopic features. Finney⁸ published the first description of PI in the United States in 1908. This case was diagnosed at surgery in a patient with an obstructing gastric carcinoma. Finney believed that PI itself represented a distinct and very rare tumor, a theory now discredited. Gazin et al.^{9,10} reported the first case diagnosed before operation by x-ray and confirmed by surgery and histologic study.

Although more than 350 case reports of PI have been published, there is a lack of information regarding the clinical management and predictors of outcome of these patients. Managing patients with PI can be challenging because urgent surgery is required in those patients with bowel infarction. On the other hand, many patients with PI have a benign course and can safely avoid surgery. A prospective evaluation of all patients with PI at Duke University Medical Center and the Durham VA Medical Center was therefore performed during a 1-year period to obtain information that would prove to be useful in management decisions.

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Methods

During a period of 1 year at Duke University Medical Center and the Durham VA Medical Center, there were 27 patients with radiographic evidence of PI. One patient had two episodes of PI with radiographic resolution between them. Another patient had three episodes with the first two treated with bowel resection. However, for the purpose of this study, each patient was counted only once. Newborns with necrotizing enterocolitis were excluded from study because this appears to be a distinct clinical entity. All x-rays were reviewed by a single gastrointestinal radiologist (RPR). To examine the correlation between clinical findings and the need for surgery and clinical outcome, six parameters of the history and physical exam were graded as either absent, mild, moderate, or severe (0, 1, 2, or 3+). These included pain, diarrhea, fever, tenderness, blood per rectum, and hypotension. The sum of these scores served as an index of the severity of the patient's clinical condition. In addition laboratory values were obtained on the day of diagnosis of pneumatosis, including WBC, pH, bicarbonate, AST, ALT, alkaline phosphatase, lactic acid, and amylase.

Patients were entered into the series at the time of the initial radiographic diagnosis of PI. At the end of 1 year, the films were all reviewed and evaluated in terms of the documented duration of the PI, the distribution of the PI, whether the PI was linear and tangential to the bowel wall or circumferential, the degree of PI (1, 2, or 3+), whether diagnosed on plain films of the abdomen or CT or both, and whether there was portal venous gas in addition to gas in the bowel wall.

Clinical and radiographic features of the 27 patients were analyzed for correlation with the presence or absence of necrotic bowel and outcome.

Results

There were 13 male and 14 female patients. The mean age of the group was 51 years, with an age range of 1

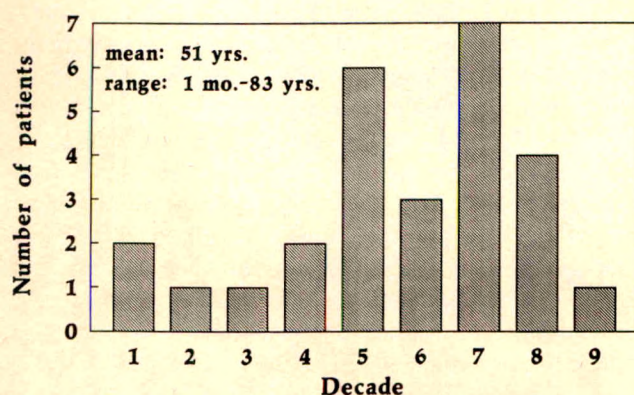


FIG. 1. Age distribution of 27 patients with pneumatosis.

TABLE 1. Diagnoses of 27 Patients with Pneumatosis Intestinalis

1. Bowel obstruction	9
Gastrointestinal tumors	5
Chronic peptic ulcer	1
Fecal impaction	1
Ileus without mechanical obstruction	2
2. Ischemic bowel	8
Hypotension	4
Mesenteric thrombosis	2
Mesenteric emboli	1
Mesenteric trauma	1
3. Trauma to bowel wall	3
4. Hepatitis/hepatic cancer	3
5. Cancer chemotherapy	2
6. Inflammatory bowel disease	1
7. Primary pneumatosis intestinalis	1

month to 83 years. Most patients were in their fifth to eighth decade of life (Fig. 1).

The principal diagnoses of the patients are listed in Table 1. Nine patients presented with bowel obstruction. Five of these patients had known gastrointestinal tumors (3 colonic, 1 gastric, and 1 pancreatic). All five underwent surgery for relief of obstruction, and none died perioperatively. One patient with known peptic ulcer disease and Alzheimer's disease presented with gastric outlet obstruction, gross gastric pneumatosis, and gross intrahepatic portal venous air by computed tomography. After a course of nasogastric suctioning and antibiotics, his PI and gastric outlet obstruction resolved. Two patients presented with colonic dilation and PI, one due to severe fecal impaction and the other due to prolonged colonic ileus. Both were explored, found to have viable bowel, and underwent decompressive colostomy.

Eight patients had a diagnosis of ischemic bowel confirmed by surgery. The causes of their intestinal ischemia are listed in Table 1. Only two of these patients survived. Three trauma patients developed PI radiographically after laparotomy and repair of bowel injuries. All three survived without additional surgery. The only death in a trauma patient occurred in a child who presented with severe hypotension and acidosis and at laparotomy was found to have a mesenteric tear resulting in bowel necrosis.

Sixteen of the twenty-seven patients underwent exploratory laparotomy. Nine of these procedures involved bowel resection, usually for ischemic bowel (Table 2). An

TABLE 2. Surgical Procedures Performed

1. Bowel resection	
for ischemic bowel	7
for colitis	1
for recurrent tumor	1
2. Bypass of obstructing tumor	3
3. Colostomy	2
4. Open and close (not salvageable)	1
5. Negative exploratory laparotomy	1
Total	16

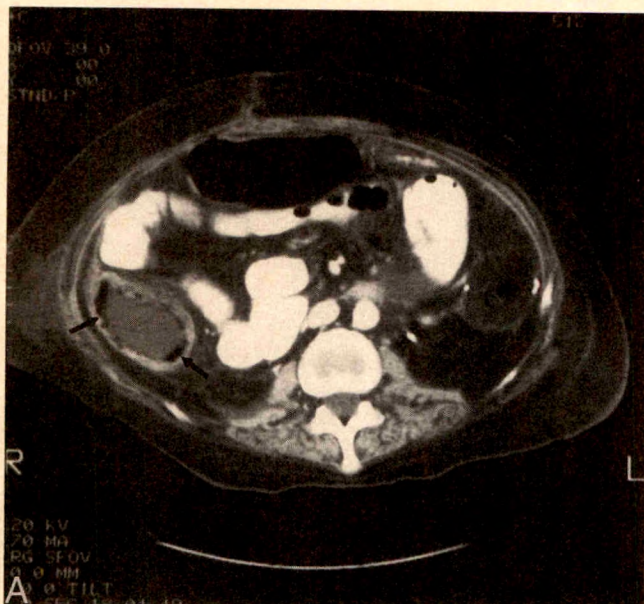


FIG. 2A. Computed tomography demonstrates pneumatosis of the right colon (arrows).

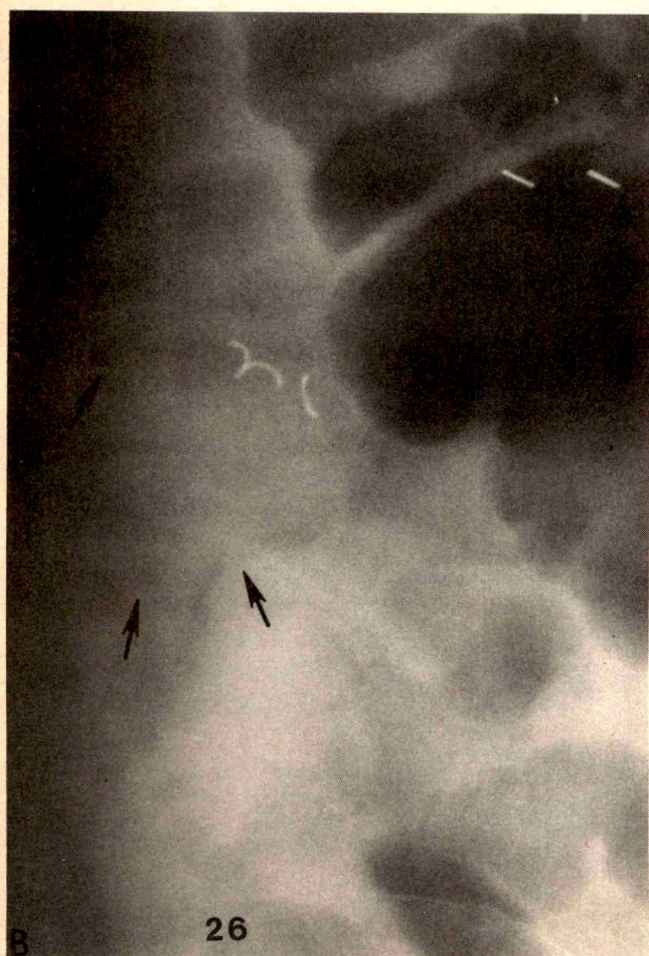


FIG. 2B. Plain film the following day shows subtle (1+) pneumatosis of right colon (arrows). At surgery the same day there was no demonstrable bowel pathology. The pneumatosis resolved after operation.

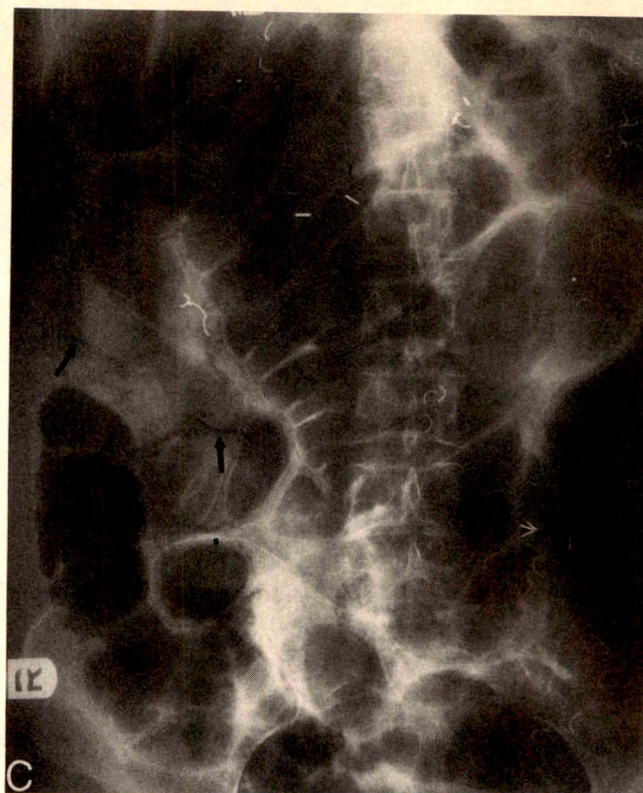


FIG. 2C. Plain film 2 weeks later again shows pneumatosis (3+) associated with gross ileus but no other significant complaints. The patient was discharged without further surgery.

obstructing tumor was bypassed in three patients. One patient was found to have necrotic bowel from the ligament of Treitz to the anus and was therefore closed and died within 24 hours. Only one patient had no pathologic findings at laparotomy despite obvious PI by plain films and CT scan (Fig. 2A and B). This patient had undergone enterolysis for small bowel obstruction 5 days earlier and also carried a diagnosis of *melanosis coli*. Her PI resolved following re-exploration but recurred 2 weeks later (Fig. 2C). The second episode was treated without operation with radiographic and clinical resolution.

Nine of the twenty-seven patients in this series died, for an overall mortality of 33% (Table 3). Eleven patients observed without surgery had a mortality rate of 18%, while those undergoing surgery had a mortality rate of 44%. The highest mortality rate was seen in patients who at surgery were found to have necrotic bowel. Six of these eight patients died perioperatively. In contrast all six patients with gastrointestinal tumors and PI required surgery and none died perioperatively. Among five patients with feeding jejunostomy tubes, there was one death due to ischemic bowel. Although a jejunostomy tube is often associated with benign PI, the patient who died was also septic, hypotensive, and died due to bowel infarction. Of the three postoperative cardiac surgical patients explored

TABLE 3. Mortality by Associated Condition*

Associated Condition	N	Died	% Mortality
GI tumor	6	0	0
Bowel obstruction	9	1	11
Jejunostomy tube	5	1	20
Trauma	4	1	25
Chemotherapy	2	1	50
Status after cardiac surgery	3	2	66
Ischemic bowel	8	6	75
Surgery	16	7	44
No surgery	11	2	18
Overall	27	9	33

* Some patients may be included in more than one category.
GI, gastrointestinal.

for PI, one died of necrotic bowel related to prolonged hypotension, and another died due to multisystem failure not directly related to her gastrointestinal problems. One of two patients with PI who was being treated with chemotherapy died, but death was due to brain metastasis. Two patients with hepatitis who were receiving lactulose developed PI. Neither developed clinical signs of an acute abdomen, and neither required surgery.

Of the two patients who died without surgery, one had known lung cancer metastatic to brain and his family requested that no surgery be performed. Autopsy was not done in this case and the viability of the bowel was therefore not determined, although necrosis was strongly suspected. The second nonsurgical death occurred in a patient with fulminant hepatitis who died of liver failure. Autopsy showed normal bowel. The nine patients who improved without surgery did not manifest any clinical signs that would have prompted laparotomy.

Indices of severity of illness correlated closely with clinical outcome. No patient with a severity of illness score of less than 4 had necrotic bowel and all survived. Patients with an intermediate score⁵⁻⁷ had necrotic bowel in two of seven cases, and six of seven survived. Patients who appeared by history and physical exam to have acute abdominal crises, with a total score 8 or more had the highest incidence of necrotic bowel, and only three of nine survived (Table 4).

Acidosis with a pH of less than 7.3 was associated with necrotic bowel in five of six patients, three of whom died. Only 2 of 14 patients with a pH of more than 7.4 had necrotic bowel. Similarly metabolic acidosis indicated by serum bicarbonate level less than 20 was predictive of necrotic bowel in 7 of 10 cases with a 40% survival. This is in contrast to patients with bicarbonate level of more than 20, who fared better, with only 1 of 16 cases having necrotic bowel (Table 4). An elevated lactic acid level also correlated with necrotic bowel and diminished survival compared to patients with a normal serum lactate level. Finally hyperamylasemia of more than 200 occurred in

three patients and all three had necrotic bowel. However most patients with necrotic bowel did not develop hyperamylasemia. The WBC, AST, ALT, and alkaline phosphatase levels had virtually no predictive value for the presence of dead bowel or for survival.

Radiographic Features of Pneumatosis

The duration of radiographically demonstrable PI varied from 1 to 21 days. Thirteen patients had PI that was demonstrable on only one day, although in most cases there were multiple films documenting the radiologic diagnosis. Three patients had documented PI for 2 days and another three patients had it for 3 days. Seven patients had demonstrable PI for 6 days or longer and each of these patients survived without surgical resection of the involved bowel.

In general the distribution of PI corresponded with the abnormality in those patients who had surgery. Fifteen patients had gross (3 plus) PI (Fig. 3). In only two of these patients was ischemia the proved etiology for the PI. In another three patients ischemia may have played a role. One of these patients had a decompressive cecostomy for a grossly distended cecum; another patient died without surgery but had severe hypotension associated with status epilepticus and generalized metastatic disease; a third patient was explored without demonstrable bowel infarction, but subsequent barium examinations suggested the probability of intestinal ischemia without full-thickness infarction. The remaining 10 patients with gross PI survived the episode without surgical resection.

In four patients the PI was rather subtle (1 plus). Three of these patients had surgical confirmation of infarcted bowel with resection, and the fourth patient had confirmation of the presence of PI by computed tomography.

TABLE 4. Correlation of Clinical and Laboratory Values with Presence of Ischemic Bowel and Outcome

	Necrotic Bowel	Survival
Clinical Severity Score		
<4	0/10	10/10
5-7	2/7	6/7
≥8	6/9	3/9
pH		
>7.4	2/14	10/14
7.3-7.4	1/2	1/2
<7.3	5/6	3/6
HCO ₃ (mmol/L)		
<20	7/10	4/10
≥20	1/16	14/16
Lactic Acid (mmol/L)		
≤2	1/8	6/8
>2	4/7	3/7
Amylase (Iu/L)		
<200	4/21	18/21
>200	3/3	1/3

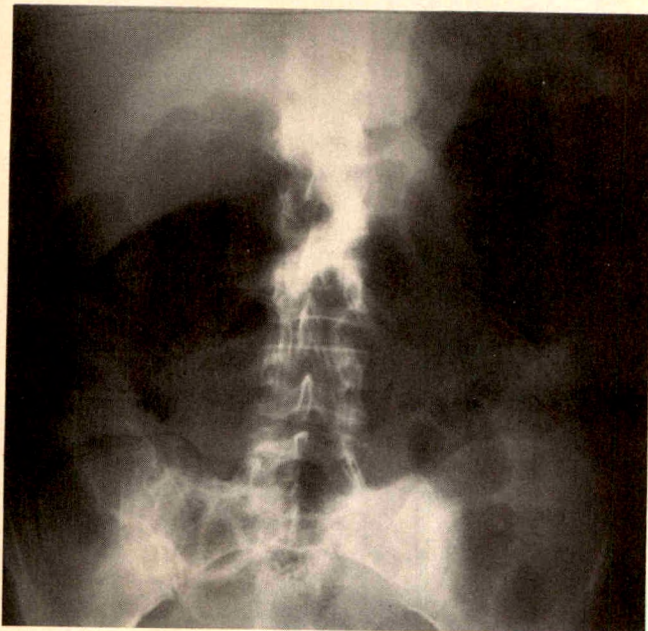


FIG. 3. Abdominal radiograph demonstrates gross linear pneumatosis (3+) involving most of the colon. This persisted for 2 weeks without significant abdominal symptoms. The patient was on lactulose for toxic hepatitis secondary to chemotherapy for malignant melanoma.

In this patient PI persisted for 8 days and was associated with chemotherapy and partial bowel obstruction.

Pneumatosis intestinalis is most conspicuous when a linear collection of gas runs tangentially along the bowel wall. Circumferential PI following the course of the valvulae conniventes may be less obvious radiographically (Fig. 4). Fourteen patients had a linear distribution of gas only, four patients had circumferential lucencies only, and in eight patients there were radiographic findings of both linear and circumferential PI. In one patient the PI was demonstrable by CT only. This patient had a gastrostomy tube and multiple enterotomies with postoperative ileus following a gunshot wound. A plain film of the abdomen 1 day after the computed tomographic examination did not demonstrate PI. Computed tomography is more discriminating in the recognition of subtle gas lucencies than are plain radiographs.¹¹

Portal venous gas may or may not be present in association with PI. In this series of 27 patients with PI, there were 11 patients in whom there was demonstrable portal venous gas. Four patients had definite ischemic disease with infarcted bowel resected surgically, two patients probably had ischemic disease, and the remaining five patients had definite portal venous gas but survived the episode without surgical resection. Two of these patients had gross gastric pneumatosis associated with gastric outlet obstruction and gross portal venous gas. Both the gastric pneumatosis and the portal venous gas resolved promptly with nasogastric tube decompression of the stomach.

Discussion

Two basic mechanical features characterize the majority of cases of PI: mucosal injury, the most important and prevalent feature, and increased intraluminal pressure. Increased intraluminal pressure may be produced by bowel obstruction, ileus, or iatrogenically by upper or lower GI endoscopy.^{12,13} Potential causes of mucosal injury are multiple and most reports of PI involve one or more of these agents. The mucosa of the GI tract is highly sensitive to ischemia and mesenteric ischemia of any etiology may result in PI.¹⁴ Enteritis of viral, bacterial, or fungal etiology may precede its onset.^{15,16} Gas-forming organisms invading the bowel wall may produce PI. Iatrogenic trauma to the gastrointestinal mucosa from either sclerotherapy, endoscopy, placement of a feeding jejunostomy tube, or surgical trauma from a gastrointestinal anastomosis may be associated with PI.^{13,17,18} Inflammation of the mucosa secondary to inflammatory bowel disease, graft-versus-host disease, and connective tissue

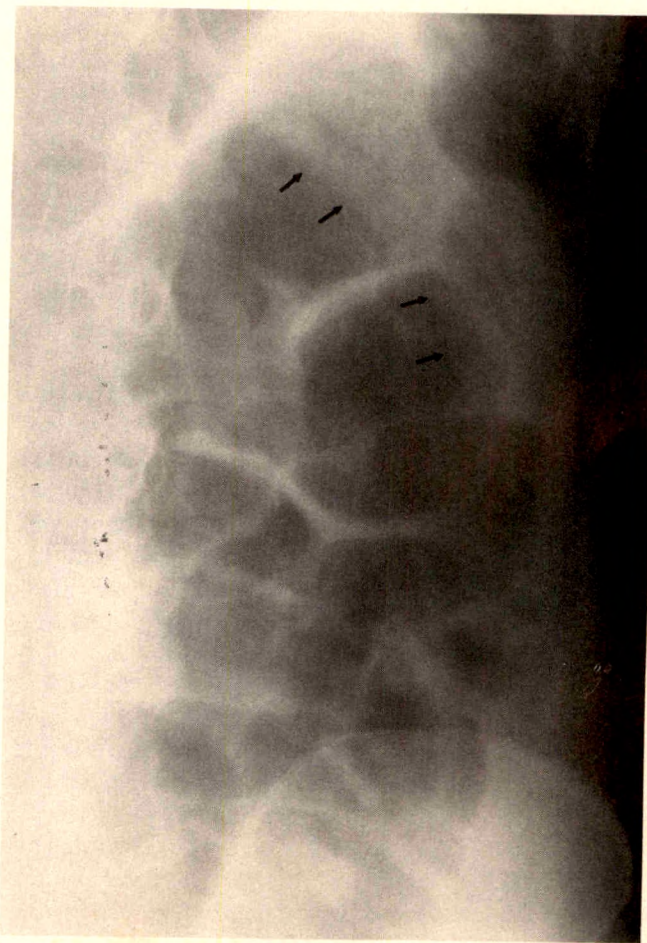


FIG. 4. A coned radiograph of the left upper quadrant demonstrates subtle (1+) circumferential pneumatosis of jejunal segment. At surgery most of the jejunum and left colon were infarcted. The patient died 7 days after resection.

diseases may be associated.^{13,19,20} Radiation enteritis or ingested corrosive agents may damage mucosa.¹³ Multi-agent chemotherapy, high-dose steroid administration, lactulose, and bone marrow transplantation have all been implicated.²¹⁻²³ Ulceration, either of the benign peptic form or by malignant gastrointestinal tumors, may precede PI. Sometimes PI may be due to pulmonary alveolar rupture with dissection of gas along retroperitoneal routes to the bowel wall. Only 1 of the 27 cases in our series lends itself to this explanation.

The frequent occurrence of PI with 27 cases at one medical center within 1 year suggests that the condition is more common than generally appreciated and that it may be underdiagnosed. Surgical consultation is frequently sought for the patient with either symptomatic or asymptomatic PI. Because the condition ranges from a benign condition requiring no specific therapy to a grave clinical problem requiring emergent surgery, factors that correlate with outcome may be useful to the clinician.

In this series PI was evenly distributed throughout the gastrointestinal tract and location did not correlate with gravity of disease. Presence of gross PI usually implied a benign clinical course. The presence of portal venous gas was associated with 37% mortality.

Patients with a radiographic diagnosis of PI should have a careful history and physical examination, which, along with knowledge of the patient's underlying disease, provide most of the information regarding need for exploratory laparotomy. Generally patients with severe abdominal pain or tenderness associated with diarrhea, blood per rectum, fever, or hypotension had abdominal surgery in this series. In addition the presence of metabolic acidosis, particularly lactic acidosis, and markedly elevated serum amylase suggest the presence of ischemic bowel. Patients whose preoperative diagnosis suggested ischemia as the primary cause of PI were more likely to have bowel necrosis than those whose PI resulted from bowel obstruction. Patients with ischemic bowel had the poorest prognosis, but the 25% salvage rate supports the role for aggressive surgery in these patients. Patients with gastrointestinal tumors or obstruction did well with surgery.

Pneumatosis intestinalis may occur after mucosal injury of any etiology, often combined with increased intraluminal pressure. Patients manifesting symptoms or signs of abdominal distress merit an aggressive surgical approach. Associated acidosis and hyperamylasemia suggest necrotic bowel and portend a grave prognosis. The finding

of PI radiographically without associated clinical evidence of intra-abdominal pathology does not necessitate operative exploration. These patients may be followed expectantly.

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Survival Following Locoregional Recurrence After Breast Conservation Therapy for Cancer

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We postulated that locoregional recurrence after limited surgery and radiotherapy for breast cancer might be associated with an additional survival hazard, similar to that of a second primary tumor with the same extent of local and regional disease. Using this hypothesis we examined the likely resultant effect on survival. Our calculations indicated that no statistically significant survival deficit due to such recurrence would be detectable until a randomized controlled trial comparing breast conservation with mastectomy had monitored more than 10,000 patients for more than 10 years. A simple mathematical model predicted 5-year survival rates in a cohort of patients treated with breast conservation of 75%, compared to 83% in those without locoregional recurrence. From the date of locoregional recurrence, a 61% 5-year survival rate was predicted, compared to 83% if no hazard was associated with locoregional recurrence. These predictions were compared with the actuarial survival rates of 499 patients with unilateral breast cancer, 49 of whom had developed locoregional recurrence. From the date of initial treatment, the 5-year survival rate of those whose disease recurred was 79%, compared to 88% for those without locoregional recurrence ($p = 0.19$). The actuarial 5-year survival rate from the date of locoregional recurrence was 63%. The similarity between the patient data and the predictions of the mathematical model indicates that locoregional failure after breast conservation therapy may result in reduced survival. The lack of a significant survival deficit in our cohort or in controlled trials comparing breast conservation therapy with mastectomy is compatible to the small size of the overall effect.

A CHEST WALL recurrence after total mastectomy for breast cancer usually heralds the development of detectable metastases.¹ In contrast recurrence in the breast after breast conservation therapy does not necessarily denote the onset of life-threatening systemic disease. Patients can expect a disease-free survival in excess of 50% at 5 years after a breast tumor recurrence is effec-

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tively treated by wide local excision or mastectomy.²⁻⁸ Such a local recurrence may be difficult to distinguish from a second primary on the basis of clinical features, histology, and, most importantly, subsequent outcome.

Studies comparing different primary treatment modalities for breast cancer have shown no consistent survival advantage for more extensive surgery or adjuvant radiotherapy,⁹⁻¹³ although local control is improved. No reproducible effect on survival has been demonstrated in a randomized controlled surgical trial comparing breast conservation therapy with mastectomy.¹⁴⁻¹⁷ Some investigators have concluded, therefore, that survival is independent of local treatment and that a local recurrence is a cosmetic failure with no impact on survival. Others believe that, although it may be too small to measure easily, there may yet be a survival deficit due to locoregional relapse.¹⁸

The probability of metastasis from a primary breast cancer is related to tumor size, nodal involvement, and such clinical features as skin invasion and chest wall involvement. We reasoned that these same prognostic factors might be predictive of additional metastatic risk in patients with a local or regional failure after breast conservation therapy. We used calculations based on this hypothesis to determine whether any of the published randomized controlled trials could have detected a relative decrease in survival (survival deficit) of this magnitude. We then calculated the probable effect of locoregional failure on the clinical course of breast conservation therapy patients treated at this institution.¹⁹ The hypothesis was validated by directly comparing the theoretical predictions of survival outcome with the actual survival curves of these patients.

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Patients and Methods

Patients

The data set consisted of women treated for early breast cancer (stage 0–II; T_{0-2} , N_{0-1}) at the M. D. Anderson Cancer Center from 1955 to 1985, staged according to the 1988 American Joint Committee on Cancer classification.²⁰ Four hundred ninety-nine of these patients were treated for unilateral tumors with breast conservation, which included local excision of the primary tumor or, in later years, segmental mastectomy and axillary dissection, followed by irradiation. The treatment details have been reported elsewhere.²¹ Median follow-up is now 5.3 years, and detailed information is available on the incidence, timing, site, and size of locoregional failures, and the subsequent clinical course.²¹ Forty-nine patients have developed locoregional recurrence; their subsequent follow-up is for a median of 27 months.

Calculations

Sample size in randomized trials. Formula 25 from Lachin²² can be used to estimate the sample size required for a randomized controlled trial comparing mastectomy with breast conservation therapy to determine if the excess locoregional failure associated with the latter has the effect on survival rate predicted by our model. For simplicity chest wall recurrence after mastectomy is equated with metastasis. Consider a hypothetical 10-year prospective randomized controlled trial to compare one treatment (mastectomy) with another that allows a 10% excess locoregional recurrence rate (breast conservation). If it is assumed that all the recurrences occur at 3 years,^{4,7,21,23} the first 3 years of patient accrual do not contribute any survival difference related to local failure; therefore the 10 years of study must start after 3 preliminary years, during which time patients are already being enrolled. If the proportional hazard for patients with locoregional control is taken to be 0.004/month (equivalent to a 5-year survival rate of 78.7%, which is plausible for patients with early breast cancer) and the additional hazard associated with locoregional failure is the same, increasing the hazard to the patient to 0.008 after recurrence, the average hazard for the 100% control group remains 0.004 while that for the 90% control group becomes $[(0.9 \times 0.004) + (0.1 \times 0.008)] = 0.0044$. We can assume that patients are accrued at random during the period of the study, and 100% follow-up is achieved until the end of the accrual period. A one-sided test is appropriate because it is unlikely that survival will be improved by locoregional failure, a power of 0.8 is reasonable,²⁴ and $p \leq 0.05$ can be understood to mean that the survival rates of the two groups are different.

The calculation predicts that 12,700 patients would be needed over the total of 13 years of this hypothetical trial

to demonstrate a statistically significant difference in survival rate. A study with patient numbers equal to or greater than this; with a comparable or longer follow-up period; or a treatment that allowed a greater than 10% locoregional recurrence rate, earlier recurrences or recurrences with a higher equivalent stage might show a statistically significant survival rate deficit.

Predicted survival curves. A mathematical model was used to predict survival rates on the assumption that a locoregional recurrence is associated with an independent metastatic risk of the same magnitude and time course as that due to a similar primary tumor. A locoregional recurrence is clearly not really independent of the preceding primary tumor, but because it may behave in a way indistinguishable from that of an ipsilateral second primary, this assumption was deemed acceptable. First actuarial survival curves from historical patients treated here and elsewhere were used to estimate the hazard rate associated with each primary disease stage. (The hazard rate is defined as the probability of dying in a period of time after having already survived until the beginning of that period and is related to the actuarial survival). The absolute values used in the calculations were not critical, providing that higher-stage disease was assigned a higher numerical risk and the values chosen were approximately appropriate; those used are listed in Table 1. Increasing the hazard rates assigned to stage 0 to III tumors by 20% decreases the predicted proportion of patients surviving at 5 years from the date of locoregional failure by only 6%. Similarly decreasing the assigned rates by 20% increased the predicted 5-year survival rate by 7%. Each primary tumor stage was assigned an appropriate hazard rate.

The size, nodal involvement, and other clinical features of a locoregional recurrence were then used to assign a stage to each recurrence. For example a recurrence in the breast that measures less than 2 cm in diameter and without positive axillary nodes was equivalent to a stage I primary; a larger breast tumor or involved axillary nodes was equivalent to a stage II primary, and recurrent disease involving the skin or chest wall, or fixed or matted axillary nodes was considered equivalent to stage III. Most of the patients suffered only one locoregional relapse; therefore, for simplicity, only the first locoregional failure was con-

TABLE 1. Hazard Rates and Corresponding 5-year Survival Rates Assigned to Patients with Stage 0 to III Breast Cancer

Stage	Hazard Rate (λ) Per Month	5-year Survival Rate (%)
0	0.00085	95
I	0.00271	85
II	0.00414	78
III	0.00996	55

sidered, and each was assigned a hazard rate according to its stage.

Survival was assumed to be an exponential function because extensive historical evidence shows that this provides a reasonable summary of survival experience:

$$p = e^{-\lambda t} \quad (1)$$

where p is the probability of surviving, λ is the hazard rate and t is time. The value of λ is thus defined for a particular group of patients by their actuarial survival rate: if the group has an average hazard rate of 0.0037 per month, the corresponding 5-year survival rate will be 80%

$$\text{5-year survival rate} = e^{-(0.0037 \times 60)} = 0.8.$$

A single patient who has two simultaneous tumors with hazard rates λ_1 and λ_2 can be expected to have a chance of being alive at time t of:

$$p = e^{-\lambda_1 t} \times e^{-\lambda_2 t} \quad (2)$$

because the overall probability of survival is given by the product of the probabilities related to independent contributing events. If, however, the second tumor occurs after an interval of time t_R :

$$p = e^{-\lambda_1 t} \times e^{-\lambda_2 (t - t_R)} \quad (3)$$

For a group of n patients, each with two tumors, the proportion, P , alive at time t is the average of the individual probabilities:

$$P = \left(\sum_{i=1}^n e^{-\lambda_{1i} t} \times e^{-\lambda_{2i} (t - t_R)} \right) / n \quad (4)$$

This fourth formula summarizes the overall effect of the hazards related to the primary tumors of all members of the group, each combined at the appropriate interval in time with the hazards associated with the second tumors, the locoregional recurrences. (The same mathematical formula would apply for a contralateral second primary.) The values of p at intervals in t can readily be calculated using a small computer.

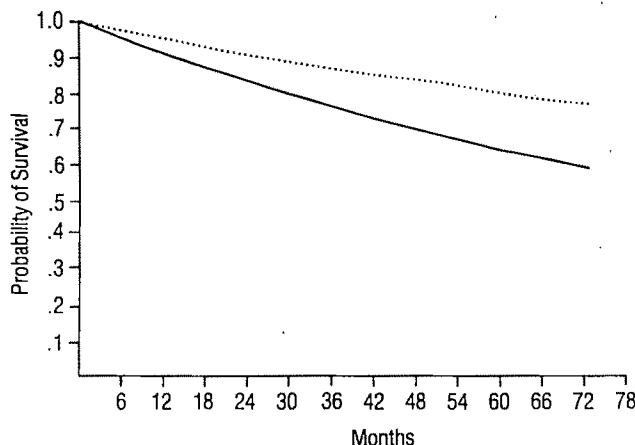


FIG. 1. Predicted chance of survival after diagnosis of a single tumor (upper curve) and two similar simultaneous tumors (lower curve).

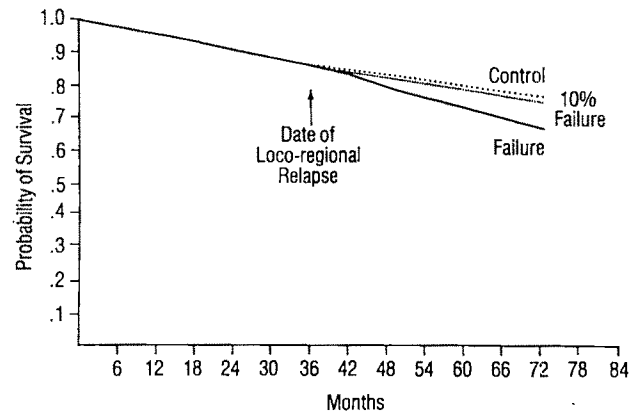


FIG. 2. Predicted chance of survival after initial tumor diagnosis. Upper curve: predicted survival probability after a single tumor. Lower curve: predictions when each patient has two tumors, the second occurring after 3 years. Middle curve: average chance of survival for a group of patients with tumors, of whom 10% develop a second tumor after 3 years.

A simple example of the effect is provided for a case in which the primary tumor is stage I and a second stage I tumor occurs simultaneously. Figure 1 compares a survival curve of this form with that belonging to the same hypothetical patient as if she had only one tumor. In Figure 2 the effect of a delay between one tumor and the other is illustrated, mimicking locoregional failure at 3 years. As expected the curves do not begin to diverge until the time of recurrence. In actuality, of course, most patients do not suffer a local or regional recurrence. The dotted line on Figure 2 shows the effect if only 10% have such a recurrence.

Using equation 4 and the details of the local and regional disease in our patients treated with breast conservation therapy (the known primary tumor stages, the equivalent stages of the locoregional recurrences that developed, and the intervals from the time of initial treatment at which failure was detected), we were able to model for that group of patients the predicted effect of locoregional failure on survival.

With the same logic, survival following locoregional failure can be described by the average of the products of the exponentials relating to the primary and recurrent tumors:

$$P = \left(\sum_{i=1}^n e^{-\lambda_{1i} t} \times e^{-\lambda_{2i} t} \right) / n \quad (5)$$

where t now represents time from recurrence.

Results

Clinical Data

In 499 treated breasts, 49 locoregional failures have occurred to date; the median time to failure was 42 months

(range, 12 to 120 months). The cumulative risk approximates 2% per year, so that for the patients who have been monitored for 10 years or more the actuarial failure rate was 19%. Overall, at 64 months median follow-up, the crude locoregional failure rate was 10%.

The majority of locoregional recurrences (84%) were confined to the breast, axillary nodes, or both. The remaining eight patients had extensive breast recurrence with chest wall involvement. Staging of locoregional failures, therefore, could be performed as for primary disease. Those that were confined to the breast, axilla, or both could be classified as T₀₋₂, N₀₋₁, stages 0 to II. The minority, involving skin or chest wall or fixed axillary nodes, were classified as T₄, N₂, stage III. A total of 16 patients had stage III recurrences, five because of involvement of the breast skin, three with fixed axillary nodes, and eight with extension of the breast tumor onto the chest wall. Table 2 lists the primary and recurrence stages for patients with unilateral disease. Although a few patients had recurrences of a lower stage than the original primary, most had more advanced disease. For example all four failures after treatment of *in situ* breast cancer were invasive. Advanced, stage III recurrence usually developed only in patients with a stage II primary; only two had a previous stage 0 or I tumor.

All recurrences were treated with much the same strategy as is a primary breast cancer of the same stage, except that additional irradiation was generally inappropriate.²⁵ The sites of failure and treatment approaches used are summarized in Table 3. Surgery was generally used for resectable tumor and systemic therapy, mostly chemotherapy, as first-line treatment for more advanced disease, followed by resection if the tumor responded. Median follow-up from the date of locoregional recurrence was 27 months.

The 5-year actuarial survival rate of patients who developed locoregional recurrences was 79%, compared to 88% for those without locoregional failure. The corresponding figures at 10 years were 64% and 72% (Fig. 3). These differences do not reach statistical significance ($p = 0.19$). Although roughly comparable for stage at initial

TABLE 2. Stages* of Unilateral Primary Tumors and Subsequent Recurrences (49 patients)

Primary Stage	Number Treated	Recurrence Stage			Total
		I	II	III	
0	39	2	1	1	4
I	231	12	8	1	21
II	229	5	5	14	24
Total	499	19	14	16	49

* American Joint Committee on Cancer staging of primary disease²⁰ and equivalent stage of subsequent relapse.

TABLE 3. Sites of Disease and Treatment of Locoregional Recurrence

No. of Sites	Recurrence	Treatment of Locoregional Relapse			
		Surg	Surg + Syst	Syst	None
33	Breast only	23	10		
5	Breast + axilla	1	4		
3	Axilla without breast		2	1	
8	Chest wall + breast		3	4	1*
49	Total	24	19	5	1

* One patient refused treatment.

Surg, surgery (wide local excision 6, simple mastectomy 18, modified radical mastectomy 14, radical mastectomy 1, wide excision of breast ± chest wall 3, axillary dissection 1, debulking 1).

Syst, systemic therapy (chemotherapy 18, tamoxifen 3, both 5, chemotherapy + estrogens 1, chemotherapy + oophorectomy 1).

treatment, age, tumor site, and so on, the average initial stage in those who failed is slightly higher than that of those who did not. This may account, at least in part, for the trend toward reduced survival in those patients with locoregional recurrence. However, in a separate study, we have identified two matched controls for each patient with locoregional failure and comparison of the survivals of these groups shows the same pattern: the 5-year survival rate of those failing was 79% ($\pm 6\%$ SE) compared to the control value of 88% $\pm 3.5\%$ (SE). From the date of locoregional failure (rather than the date of initial treatment), the 5-year survival rate of the 49 patients with locoregional recurrence was 63% (Fig. 4).

Calculated Survival Curves

Of the 49 patients with unilateral breast cancer who had a locoregional failure, four had initially received breast

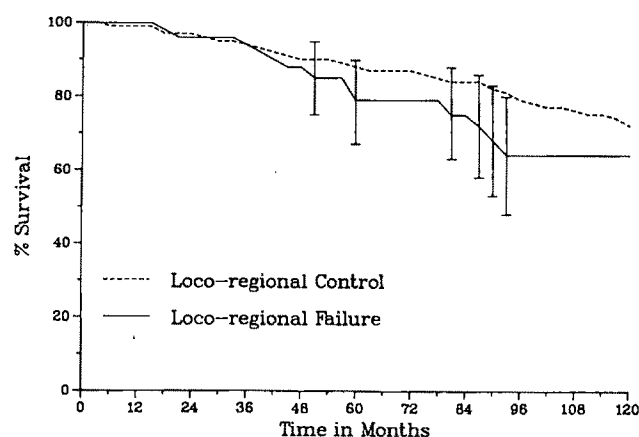


FIG. 3. Comparison of actuarial survival rates of patients whose breast cancer did and did not recur locoregionally. The vertical bars show the 95% confidence limits for the smaller group (with locoregional recurrence).

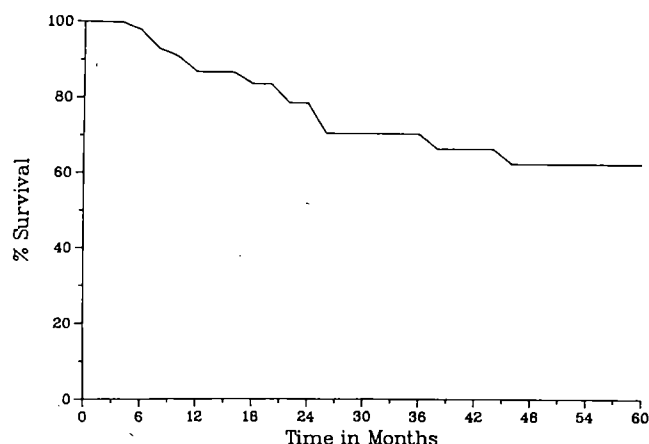


FIG. 4. Actuarial survival from the date of locoregional relapse (n = 49).

conservation therapy for stage 0, 21 for stage I, and 24 for stage II disease. None of the locoregional failures was *in situ*: 19 were equivalent to stage I, 14 to stage II, and 16 to stage III disease (Table 2).

Figure 5 shows the calculated survival predictions for these patients with locoregional failure, using equation 4. For comparison the calculated survival rates of the same group of patients as if their disease had not recurred is also plotted. The predicted difference in survival rate, due to locoregional failure, is 8% at 5 years and 20% at 10 years. Assuming that a prospective, randomized controlled trial of breast conservation therapy compared to mastectomy resulted in patterns of failure similar to those found in our patients (failure at similar intervals from treatment, recurrent disease of comparable extent, and a failure rate around 10%), the survival deficit in such a trial would be approximately 2% at 10 years because 90% of the patients carry only the risk related to the primary tumor.

The predicted 5-year survival rate from the date of locoregional failure is 61%; if these patients had not developed locoregional recurrence their calculated survival rate would be 83%, yielding a survival deficit of 22% (Fig. 6).

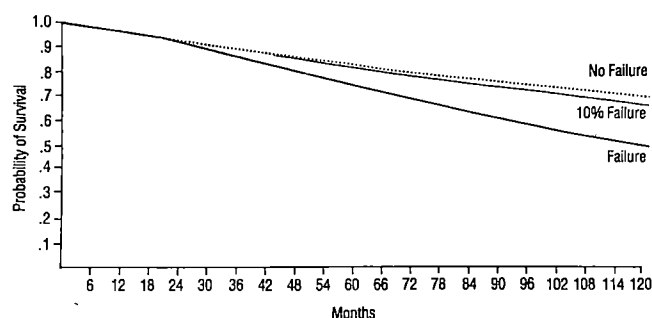


FIG. 5. Predicted survival curve for the patients developing locoregional failure (lowest line) compared to the curve calculated as if the same patients had not had such a recurrence (top line). The middle curve illustrates the prediction if only 10% of the patients develop locoregional failure.

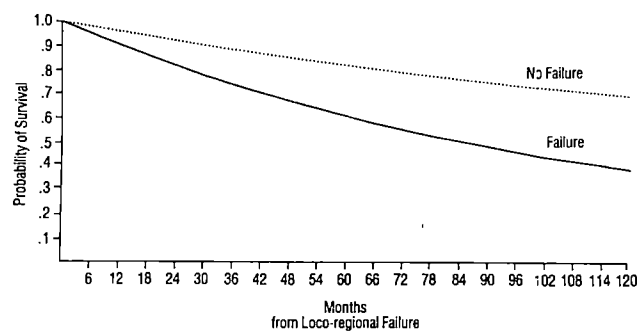


FIG. 6. Predicted survival from the date of locoregional failure (lower curve). The comparison is to predictions for the same patients as if they had not developed locoregional recurrence (upper curve).

Discussion

Our hypothesis is that there is a higher risk of death from disease for patients whose tumors relapse in the treated breast or axilla after breast conservation surgery and irradiation. The calculations predict a survival deficit for those with locoregional recurrence relative to those with locoregional control of 8% at 5 years, when survival rates are calculated from the date of initial diagnosis (Fig. 5). The actual survival curves of patients who did and did not relapse locoregionally (Fig. 3) show a trend toward a lower survival rate for those whose disease recurred, compatible with these calculated predictions. Published curves based on patients treated elsewhere also show the same pattern.^{8,23} When survival rate predictions are made from the date of locoregional relapse, a predicted additional 22% risk of death results in a 61% survival rate at 5 years (Fig. 6); the actual 5-year survival rate following recurrence in our patients is remarkably similar at 63% (Fig. 4). Because only a few patients suffer locoregional relapse, the predicted survival deficit in a randomized controlled trial comparing breast conservation therapy with mastectomy is less than 5% at 10 years. More than 10,000 patients would need to be accrued and monitored for more than 10 years to demonstrate a statistically significant difference in survival rate because the overall survival rate of patients treated by breast conservation therapy is dominated by the sustained low risk of the majority of the patients who do not have a locoregional recurrence.

Information on locoregional failure has been published from four prospective randomized trials comparing breast conservation therapy with mastectomy: two from Guy's Hospital, London;^{15,26} one from Milan;^{16,17} and the United States' National Surgical Adjuvant Breast Project's trial B-06.¹⁴ Their results are summarized in Table 4.

The largest study is B-06, which contained about 600 patients in each of three arms: lumpectomy, lumpectomy with radiotherapy, and mastectomy. The survival rates of the three patient groups are the same. The group who had lumpectomy alone had a rate of locoregional recurrence

TABLE 4. Results from Prospective Randomized Trials of Breast Conservation Therapy Versus Mastectomy

Trial	Treatment	No. of Patients	Years of Follow-up	Failures			
				BR	CW	AX	SC
Guy's I ¹⁵	WLE + XRT	180	>15	17	21	35	1
	MAST	192					
Guy's II ¹⁵	WLE + XRT	120	>11	6	12	15	3
	MAST	138					
Milan ^{16,17}	QUART	352	8.5 average	7	7	2	5
	MAST	349					
B-06 ¹⁴	L	636	7.75	175	46		46
	L + XRT	629	average	39	7		28
	MAST	590					

BR, breast; CW, chest wall; AX, axilla; SC, supraclavicular nodes; WLE, wide local excision; XRT, radiotherapy (doses used, areas treated

and modality varied); MAST, mastectomy; QUART, quadrant excision, axillary dissection and radiotherapy; L, lumpectomy.

substantially higher than 10%: 175 failures in the breast, 46 in the chest wall, and 46 regional nodal relapses (42% overall at 8 years). Nevertheless patient numbers are insufficient for the study to be expected to show a significant survival difference. Although the numbers of patients included in this trial are larger than in any other, and the locoregional failure rate in the surgery-only arm is higher, even with further follow-up a survival difference due to locoregional failure is not likely to be detectable.

The study with the longest follow-up is the first Guy's trial, in which a total of 372 patients were randomized to wide local excision plus radiotherapy, or mastectomy. At the latest update, minimum follow-up was probably in excess of 15 years, by which time 17 breast recurrences and 35 axillary recurrences had developed, 29% overall (the axilla was not dissected and the radiotherapy dose used was low by current standards).¹⁵ Again a statistically significant survival deficit would not be expected from our hypothesis, and none was found. The second Guy's trial, however, resulted in a significantly higher survival rate for those treated with mastectomy, and subsequent analysis has indicated that the difference was largely related to the higher survival rate for patients with stage I tumors treated by mastectomy.¹³ This study, now at 11 years follow-up, had fewer patients than the first (total 258) but a more homogeneous patient population: accrual was restricted to patients with T_{1-3A}, N₀ tumors. It is nevertheless possible that, with arms containing less than 150 patients, there may have been important differences between the patient groups at randomization that led to differences between the survival curves. Such differences would become progressively more obvious during the follow-up and would lead to spurious statistical significance.^{27,28}

The most recent update of the Milan trial, in which patients with T₁, clinical N₀ tumors were randomized to mastectomy (most had radical mastectomy) or quadrantectomy, axillary dissection and radiotherapy (QUART), has 349 and 352 patients in each arm, an average follow-

up of 8.5 years, and 7 breast failures reported in the QUART arm. There is no significant survival difference between the treatment arms.

Thus no randomized prospective study comparing breast conservation therapy with mastectomy to date has the statistical power to demonstrate a survival deficit due to locoregional failure if it is of the magnitude of that associated with a comparable primary, and no reproducible survival difference has been demonstrated. Application of our model to the combined results of the four randomized controlled trials comparing breast conservation therapy with mastectomy would be of interest. However it would require information on the timing and extent of locoregional recurrence that is not available from the published reports.

Another approach to estimating the additional risk for patients with locoregional failure is to compare them with patients with metachronous bilateral breast cancer. Contralateral breast cancers are accepted as carrying independent risks of metastasis and death. The effect is assumed to be related to the stage of the second primary, so that the prognosis for patients with bilateral tumors is understood to be dominated by that of the more advanced tumor. A recent study²⁹ included a direct comparison of the survival rates of patients treated with breast conservation therapy whose disease recurred locally with those of patients who developed contralateral tumors. Although the timing and stage of contralateral primaries were different from those of ipsilateral recurrences, so that a close match would not be expected, the similarity of the patients' actuarial curves supports the thesis that an ipsilateral recurrence carries approximately the same survival hazard as a similar contralateral primary.

Those same primary tumor features that lead to locoregional failure may also lead to metastasis and death; our model cannot prove a direct effect of locoregional failure on survival. However, in the absence of a very large randomized controlled trial, a survival deficit due to locoregional recurrence cannot be discounted. On av-

erage, locoregional recurrences in our patients were at a higher stage than that of the initial primary disease. Therefore recurrence was predicted to more than double the hazard for an individual patient. This would be of clinical importance, underlining the importance of frequent screening for early detection and effective treatment of locoregional failures after breast conservation therapy.

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Late Recurrence of Malignant Melanoma

Analysis of 168 Patients

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Analysis of 7104 patients with melanoma seen at Duke University identified 168 who experienced their first recurrence 10 or more years after diagnosis, for an incidence of 2.4%. This included patients with all stages of disease. There was no sex, age, or primary site predominance. The mean disease-free interval for cutaneous melanomas was 14.3 years *versus* 22.3 years for ocular primary melanomas. The prognosis following relapse was related to the site of recurrence. Survival after local or regional node recurrence was often prolonged; survival after distant metastases was usually limited. Patients with ocular primaries had the highest incidence of distant metastases, and the shortest subsequent survival. An additional 483 patients were identified who survived 10 or more years without evidence of recurrence; of these 651 patients with long disease-free intervals, 25% (168 of 651) developed recurrent disease. This demonstrates that a 10-year disease-free interval cannot be considered a cure, and emphasizes the importance of continued annual follow-up.

THE MAJORITY OF recurrences and deaths resulting from malignant melanoma occur within 10 years after treatment of the original tumor. Late recurrences, defined as those occurring 10 or more years after diagnosis and treatment, have been documented in the literature but are still considered an unusual clinical course. There have been three series reported in the literature dealing with the clinical characteristics of this small subgroup of patients. Briele¹ described 7 patients with late recurrences; Shaw² added the largest series of 34 patients, although pathology was only available in 21 of the 34 patients. The most recent series by Callaway³ describes an additional five patients with late recurrences. The lack of information on the patient characteristics, histopathology, and clinical courses of this small subgroup of interesting patients prompted us to examine the long-term

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survivors seen at the Duke Melanoma Clinic. We report here our series of 168 patients with late recurrences.

Patients and Methods

Since its inception in 1970, the Duke University Melanoma Clinic has registered 7104 patients. A retrospective computer-aided search identified 168 patients who had a disease-free interval of 10 or more years, with a subsequent recurrence. This yields an incidence of approximately 2.4%. Patients with multiple primaries ($n = 4$) were excluded. One hundred two patients of the 168 total had pathologic records available from their original primary. The remaining 66 patients did not have complete pathologic records, but did have the diagnosis of melanoma confirmed by histologic examination of their recurrent disease. For comparison the computer-aided search also identified a total of 483 patients who had survived 10 or more years, and still had no evidence of recurrence.

In most cases the initial treatment consisted of wide local excision with primary closure or split-thickness skin graft, as indicated by the location of the primary. One exception was a patient who presented with a solitary lung nodule and an unknown primary; she was treated by resection of her isolated nodule. In addition a subset of patients underwent an elective lymph node dissection (ELND) as part of their initial management. Eleven patients had tumor-involved nodes on pathologic examination and are classified as stage II disease. An additional 17 patients with stage I disease underwent ELND; the remaining 139 patients had clinical stage I disease and did not have an ELND performed. Patients with ocular melanomas were treated by enucleation.

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Results

The clinical characteristics of the 168 patients are presented in Table 1. Fifty-three per cent of the patients were female and 47% were male. All patients were white. The mean age at diagnosis was the same for male (39.5 years) and female (39.6 years) patients. Ninety-three per cent of patients presented with stage I disease, with only 11% undergoing an elective lymph node dissection. Six per cent of patients presented with stage II disease, with one to three involved nodes seen on pathologic examination. Only one patient presented with stage III disease; this patient presented with a solitary lung nodule and an unknown primary lesion. The majority of primary lesions were located on the extremity in female patients (59.6% of female and 17.7% of male patients) and on the trunk in male patients (58.2% of male and 23.6% of female patients). The number of head and neck primary lesions (10.1% of female and 15.2% of male patients) and ocular primary lesions (5.6% of female and 8.9% of male patients) were similar for the two groups.

The pathologic characteristics are shown in Table 2. The majority of patients had Clark's level III and IV lesions, although there were patients with lesions in all levels. Breslow measurements were available in 67% of patients (the remaining patients had Clark's level only). The majority had lesions of intermediate (1.0 to 3.0 mm) thickness (56.7%), with a mean of 1.6 mm and a range of 0.34 mm to 6.3 mm. By histologic classification, superficial spread-

TABLE 1. Population Characteristics

Sex (number of patients; percentage)					
	Male				79 (47.0%)
	Female				89 (53.0%)
Primary (number of patients; percentage)					
Site	Trunk	Extremity	Head/neck	Unknown	Ocular
Number	67 (39.9%)	67 (39.9%)	21 (12.5%)	1 (0.6%)	12 (7.1%)
Male	46	14	12	0	7
Female	21	53	9	1	5
Age at Diagnosis (number of patients; percentage)					
	10-19 yrs.				8 (4.8%)
	20-29 yrs.				26 (15.5%)
	30-39 yrs.				51 (30.3%)
	40-49 yrs.				42 (25.0%)
	50-59 yrs.				29 (17.3%)
	60-69 yrs.				11 (6.5%)
	70-80 yrs.				1 (0.6%)
Stage of Disease (number of patients; percentage)					
	Stage I				156 (92.9%)
	ELND				17
	No ELND				139
	Stage II				11 (6.5%)
	Stage III				1 (0.6%)

TABLE 2. Histologic Characteristics*

Clark's Level (number of patients; percentage)	
I	1 (1.1%)
II	11 (12.4%)
III	51 (57.3%)
IV	23 (25.8%)
V	3 (3.4%)
Breslow Thickness (number of patients; percentage)†	
<0.75 mm	11 (11.3%)
0.75 to 1.0 mm	9 (15.0%)
1.01 to 3.0 mm	34 (56.7%)
3.01 to 4.0 mm	4 (6.7%)
>4.0 mm	2 (3.3%)
Histologic Type (number of patients; percentage)§	
Superficial spreading	58 (65.2%)
Nodular	14 (15.7%)
Acral lentiginous	3 (3.4%)
Lentigo maligna	2 (2.2%)
Unclassified	12 (13.5%)

* Ocular and unknown primary lesions excluded; available for 89 patients.

† Available for 60 patients.

§ Available for 89 patients.

ing melanoma was the most common (65.2%), with most of the remaining lesions classified as nodular (15.7%). Ulceration of the primary lesion was present in 17% of the cases.

The distribution of the 168 patients according to disease-free interval and age at relapse is shown in Table 3. The majority of patients (48.2%) recurred between 10 and 12 years after the original primary. Another 23% recurred at 13 to 15 years, and approximately 14% between 16 and

TABLE 3. Disease-free Intervals and Age at Recurrence

Age at recurrence (number of patients; percentage)	
20-29 yrs.	3 (1.8%)
30-39 yrs.	17 (10.1%)
40-49 yrs.	40 (23.8%)
50-59 yrs.	42 (25.0%)
60-69 yrs.	50 (29.8%)
70-79 yrs.	13 (7.7%)
80-90 yrs.	3 (1.8%)
Disease-free Interval (in years; percentage of patients)	
10-12 yrs.	81 (48.2%)
13-15 yrs.	38 (22.6%)
16-19 yrs.	24 (14.3%)
20-25 yrs.	15 (8.9%)
26-30 yrs.*	5 (3.0%)
30-39 yrs.†	3 (1.8%)
40-49 yrs.§	2 (1.2%)

* Two patients had ocular primary lesions; three patients were females with extremity primary lesions.

† One patient had an ocular primary lesion; two female patients had extremity primary lesions.

§ Both patients had ocular primary lesions.

TABLE 4. Sites of Recurrence Grouped by Location of the Primary Lesion

Primary Site	Extremity (67)	Trunk (67)	Head/neck (21)	Ocular (12)
Local skin	7 (10.4%)	7 (10.4%)	3 (14.3%)	1 (8.3%)
Regional nodes/in transit	40 (59.7%)	26 (38.8%)	5 (23.8%)	0
Distant skin	2 (3.0%)	3 (4.5%)	2 (9.5%)	0
Lung	8 (11.9%)	14 (20.9%)	4 (19.0%)	1 (8.3%)
Liver	2 (3.0%)	0	1 (4.8%)	8 (66.7%)
CNS	1 (1.5%)	4 (6.0%)	0	0
Multiple sites/other*	7 (10.4%)	13 (19.4%)	6 (28.6%)	2 (16.7%)

* Including bone and GI metastases.

19 years. A total of 25 patients relapsed after 20 years. The two longest disease-free intervals were 45 and 47 years, and both occurred in patients with ocular primaries. Of the eight patients who recurred between 26 and 40 years, three had ocular primaries and five were female patients with extremity primaries. Although the longest survivors were predominantly female (9 of 10 patients), there were approximately equal numbers of male and female patients who recurred between 20 to 25 years and between 15 to 20 years. The mean time to recurrence for all cutaneous lesions was 14.3 years; the mean time to recurrence for the 12 patients with ocular primary lesions was 22.3 years.

The patterns of recurrence were examined for each primary site and are detailed in Table 4. The actuarial survival curve for all patients, by primary site, is shown in Figure 1. The majority of recurrences associated with extremity primaries were in the local skin or regional nodes (70.1%). Of these 47 patients, 19 have died (survival time, 11 months to 6.8 years), 6 have progressive disease with a guarded prognosis (5 months to 6.9 years following relapse), and 22 are currently without evidence of disease

(follow-up, 7 months to 28 years after recurrence). More than 5 years has passed since recurrence in 10 of these 22 patients, and 5 are free of disease now for more than 10 years. Of the eight patients with pulmonary recurrences, six have died (survival time, 6 to 48 months) and two are currently without evidence of disease (3.5 and 3.8 years following recurrence). The patients with other visceral metastases, metastases at multiple sites, or distant skin metastases as the presenting site of recurrence have died (survival time, 1 to 24 months) or have evidence of progressive disease (1 to 16 months following recurrence).

For axial primaries, a local skin or regional node recurrence was still the most common presenting site (49.2%); however lung metastases were also common (20.9%). The patients with local and regional node recurrences experienced the best survival. Of these 33 patients, only six have died (survival time, 5 months to 6.3 years). Twenty-seven are alive, and 22 have no evidence of disease (8 months to 17.6 years following recurrence). Seven of these patients are free from recurrence for more than 5 years, and 3 are now disease free for more than 10 years. Of 14 patients with lung recurrences, 4 have died (survival time, 4 months to 4.1 years) and 4 have progressive disease (1 to 16 months following recurrence). The remaining six patients are currently doing well without evidence of disease (follow-up time, 6 months to 7.1 years), with 4 of 6 disease free for more than 3 years since recurrence. The patients with other distant metastases had extremely short survival times (2 to 18 months) or currently have progressive disease (1 to 14 months following recurrence).

The pattern of recurrence for the patients with head and/or neck primary lesions was similar to that seen with axial primaries, although there was a shift from local and regional recurrences to recurrences at distant sites. Only 38% of these patients presented with regional disease. Of those 8 patients, 4 have died (survival time, 22 months to 4.7 years) and 4 have no evidence of disease (4 months to 3 years following recurrence). Most patients presented with distant metastases, with limited subsequent survival. Of the 11 patients with visceral metastases, 7 have died (2 to 31 months), one has progressive disease (8 months

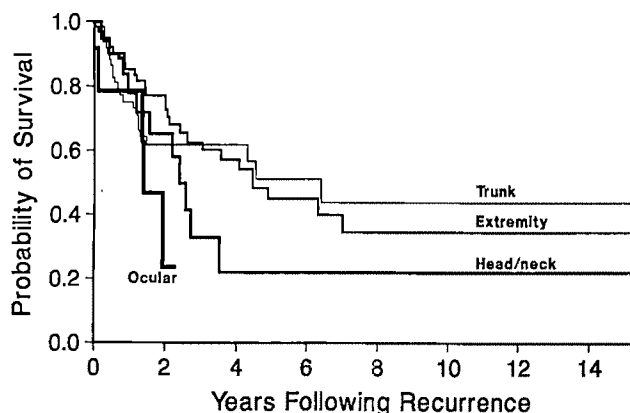


FIG. 1. Actuarial survival for all patients, by primary site. There was no statistical difference in survival between patients with extremity primaries and patients with trunk primaries. Patients with head/neck primaries tended to have a shorter survival, but this did not reach statistical significance. The shortest survival times after recurrence were in patients with ocular primary lesions ($p < 0.05$ when compared to patients with extremity lesions).

following recurrence) and only one is currently without evidence of disease (8 months after lung recurrence).

The majority of patients with ocular primary lesions experience recurrence in the liver (67%). These patients have either died or have progressive disease (range, 1 to 24 months). The other three patients with distant recurrences also have progressive disease (1 to 2 months after recurrence) or have died (survival time, 1 month). Only one patient is currently disease free (for 28 months) after having a local recurrence.

The single patient with an unknown primary lesion experience recurrence 12 years after diagnosis, with a recurrence in the lung and distant skin. This patient died from metastatic melanoma 6 months after recurrence.

The patients with stage II disease at the time of presentation tended to experience recurrence earlier than the stage I patients. These 11 patients included 5 trunk primaries (4 male, 1 female), 5 extremity primaries (2 male, 3 female), and one male patient with a head and/or neck primary. These patients recurred at a mean of 12 years *versus* 14.3 years for cutaneous stage I patients, and experienced more distant recurrences. The sites of relapse included regional nodes or local skin (2), lung (2), distant skin (1), central nervous system (2), or multiple sites (4). Seven of these patients have died (survival time, 1, 2, 2, 6, 12, 24, and 42 months) and three have progressive disease (1 to 15 months following recurrence). Only one patient (nodal recurrence) is disease free 4 years after recurrence.

The 17 patients who had ELND experienced recurrence at a mean of 13.9 years, which is similar to the mean time to recurrence for all cutaneous stage I patients. Ten of these patients had extremity lesions, and the majority still recurred locally or in the regional nodes (60%). Four patients had trunk primaries, and recurrences were divided between local skin (50%) and distant sites (50%). Three patients had head and/or neck primaries and all lesions recurred at distant sites.

Although the menstrual status of the women in the series was not specifically known, 23 of the 89 female patients were older than 50 years, and thus were presumably postmenopausal. An additional 8 patients were between 45 and 50 years old, and also likely to be perimenopausal. A total of 45 patients were less than 39 years, and therefore were likely to be premenopausal. Only one patient was pregnant at the time of diagnosis.

Discussion

Late recurrences from malignant melanoma occur infrequently;¹⁻⁷ the present study presents the clinical and pathologic characteristics of 168 patients with this unusual clinical course. Briele¹ reported a 6.7% incidence in his series of 105 patients; Shaw² reported a lower incidence at 2.7% in his series of 1283 patients; and Callaway³ reported a 0.98% incidence in a series of 536 patients. In

our series of more than 7000 patients, the incidence was 2.4%. Of note, the database also contains 483 patients who have lived 10 or more years without a subsequent recurrence. This means that for all patients who had a disease free interval of 10 or more years (651 patients), 25% had a subsequent recurrence. This significant percentage demonstrates that a 10-year disease-free interval can not be considered a cure.

There remains a considerable degree of controversy in the literature regarding factors related to a long disease-free interval. Day⁸ suggested that deaths from melanoma occurring after 5 years in patients without previous evidence of bony or visceral metastases occurred exclusively in patients with lesions measuring 1.70 to 3.64 mm in thickness. In the present series, mean tumor thickness was 1.6 mm, with a range of 0.34 to 6.3 mm. This is similar to the results of Callaway³ (mean, 1.8 mm; range, 0.81 to 3.1 mm) and Shaw² (mean, 2.0 mm; range, 0.2 to 7.4 mm), which suggests that tumor thickness is not an absolute predictor of a long disease-free interval. Not unexpectedly the majority of lesions in this series were Clark's III and IV, and very few patients had thick (more than 4 mm) lesions. Essentially all patients with deeper primary lesions would be expected to recur within 10 years.

The influence of gonadal hormones on the disease-free interval is also an area of controversy. Briele¹ and Raderman⁴ concluded from their series and literature review that premenopausal women constitute the majority of patients with late recurrences, and suggested that the endocrine system played a role in the long disease-free interval. In contrast, Shaw² and Callaway³ concluded from their series that menstrual status at the time of diagnosis was not important in predicting a long disease-free interval. The present series also fails to demonstrate any advantage for premenopausal women. Although menopausal status was not specifically known for all women, nearly 30% of patients were older than 50 years, and were presumably postmenopausal. In addition approximately one half of the late recurrences occurred in men.

Callaway³ also concluded from his series that women who present with primary lesions on their extremities seem to be at higher risk of developing late recurrences. Again the present study does not support this conclusion. There were approximately equal numbers of men with axial primaries to women with extremity primaries in this series. In addition, if one looks at patients with a 15- to 25-year disease-free interval, the number of female patients with primary lesions of the extremities (15) is still approximately equal to the number of men with axial primary lesions (13). Only in the group of patients with cutaneous primary lesions and extremely long disease-free intervals (more than 25 years) was there an absolute dominance of female patients with extremity lesions.

The clinical course after recurrence is variable but is

most closely related to the site of recurrence, rather than to the primary site. In our series most recurrences from extremity lesions were either local skin, in transit, or regional nodes (70.1%), and these patients had the best survival. Distant metastases were much less common and were associated with extremely short survival times. In contrast, trunk and head and/or neck primary lesions were associated with locoregional metastases in approximately 50% and 38% of cases, respectively; these patients had a higher incidence of distant metastases, which was often associated with limited survival after recurrence. Our data suggests that the survival subsequent to recurrence is related to the site of the recurrence rather than to the primary site or sex of the patient. Clearly those patients with local and regional metastases have the best survival after relapse; these patients are often women with extremity lesions. There was a higher incidence of distant metastases associated with trunk and head and/or neck primaries, with often limited survival. These patients were frequently male, due to the higher incidence of axial primaries in men.

Ocular primary lesions have been associated with an extremely high incidence of liver metastases,⁹ and this was confirmed in our group of 12 late recurrences. The vast majority of these patients had distant metastases at the time of recurrence (92%), the majority of them hepatic (67%). These patients had extremely short survival times after relapse. Ocular primary lesions also have been associated with long disease-free intervals, and in our series five of the longest latent periods were in this patient group (47, 45, 30, 28, and 27 years). However, because most of the recurrences are hepatic, these patients have an extremely limited survival time after relapse.

The influence of ELND on the subsequent survival of patients with late recurrences has not been clearly defined. In the series by Briele,¹ Koh,⁶ and Callaway,³ all recurrences were either local or in the regional nodes, and none of these patients had undergone an ELND at the time of primary diagnosis and treatment. However, in these series, 12 of the 14 patients had extremity primaries, and thus would be expected to experience regional recurrence. Shaw² attributed the greater degree of distant metastases in his series to the high incidence of ELND (10 of 34 patients), concluding that patients with ELND tended to recur at distant sites, with the attendant short survival time subsequent to recurrence. The incidence of ELND in this series was extremely low (11%). Approximately 60% of patients with extremity lesions who underwent ELND still had an in transit or regional nodal

recurrence. Two patients with ELND and trunk primaries also had local recurrences (50%). This distribution of recurrence is similar to that seen for all stage I patients, and again suggests the site of recurrence is influenced by the site of the primary, and not by the presence or absence of an elective lymph node dissection.

This series also reports late recurrences in stage II patients, which has not been documented in the literature. These patients had a shorter mean disease-free interval (12.0 *versus* 14.3 years), with 9 of 11 recurring at distant sites. The one patient with prolonged survival experienced a regional node recurrence, again demonstrating the influence of the site of recurrence rather than the primary lesion. We also report one case of a stage III patient who survived 12 years before recurrence; the relapse was at a distant site (lung) and associated with only 6 months subsequent survival.

The significant percentage of patients with a disease-free interval of 10 or more years who subsequently recur (25%) emphasizes the fact that a 10-year survival interval does not represent a cure. We recommend annual follow-up examinations for all melanoma patients. Examinations should include evaluation of the primary site and regional nodes; we also recommend annual chest x-ray and liver function studies because of the significant rate of recurrence in these areas. An aggressive approach is warranted because many patients do have prolonged survival times following treatment of their recurrent disease.

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Recombinant DNA and Surgery

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We have the ability to isolate DNA from tissue, determine its base-pair sequence, and ask if a gene of interest is present. DNA strands can be isolated from one type of cell or organism, cleaved, and inserted (recombined) with DNA from another cell or organism. Recombinant DNA techniques have already improved health care by providing clinically useful quantities of pure human protein hormones such as erythropoietin, insulin, and growth hormone. Furthermore these techniques may increase our understanding of cellular growth control mechanisms to a level that was previously unattainable. They will also increase our knowledge of the development of major diseases and provide a means of specific nontoxic therapies for these diseases. Surgeons will need to understand basic DNA research terminology to keep up with the revolution in medical therapies that these techniques will cause. Our purpose is to begin the process of linking surgery to DNA.

The Significance of DNA to the Surgeon

DNA and the control of its expression determines the function of the cell. DNA is the root of tissue repair and regeneration. It is also the root of cancer and other common surgical diseases. DNA research has been useful in the detection and identification of new molecules. Pure human proteins can be synthesized by DNA techniques. The underlying cause of surgical disease can be diagnosed with DNA research techniques and these techniques will change surgical practice. Therefore the surgeon's knowledge of basic DNA biology must expand.

Changes in DNA sequence within certain classes of genes called oncogenes have been associated with tumor formation. We are entering an era in which antitumor therapies will not be designed from a combination of

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judgment and statistics about each anticancer drug's effect on disease free survival. Therapies will include manipulation of gene expression. Oncogene research can identify specific base-pair substitutions in DNA sequences that make cells tumorigenic. Therapeutic agents are being designed to produce DNA sequence-specific suppression of the phenotypic expression of oncogenes. This highly specific therapy contrasts sharply with the present comparatively indiscriminant chemotherapy in which rapidly dividing cells (both neoplastic and normal) are killed.

Surgeons will continue to play an active role in the care of patients with cancer and other diseases, but they will play an enhanced role if they understand recombinant DNA language. They will have an important role in the acquisition of tissue for DNA sequence analysis, which will be needed to allow DNA sequence-specific treatment. Thorough understanding of DNA and oncogene research, however, requires a basic understanding of DNA and the techniques of DNA analysis. The purposes of this review are to discuss: (1) the theory behind recombinant DNA techniques, (2) oncogenes and their isolation, (3) oncogenes in non-neoplastic disease, and (4) the potential impact of recombinant DNA technology on clinical medicine and surgery.

The Study of DNA

DNA Fragment Isolation

The enormity of information contained within the human genome can be difficult to comprehend. To date approximately 600 of the estimated 100,000 human genes have been sequenced.¹ The human genome consists of

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three billion nucleotide base pairs. Assuming one letter per nucleotide, it would take 13 volumes of the *Encyclopedia Britannica* to list the sequence of genetic nucleotide pairs for a single human cell.² Furthermore, because there are four nucleic acid bases (cytosine, thymidine, guanine, and adenine), DNA sequences only 20 base pairs in length could exist in 4^{20} , or about 1.1×10^{12} , different configurations. This means that the study of DNA must be based on exact sequence specificity and on techniques of isolation that preserve the integrity of the DNA molecule.

DNA is double stranded (Fig. 1). It can temporarily

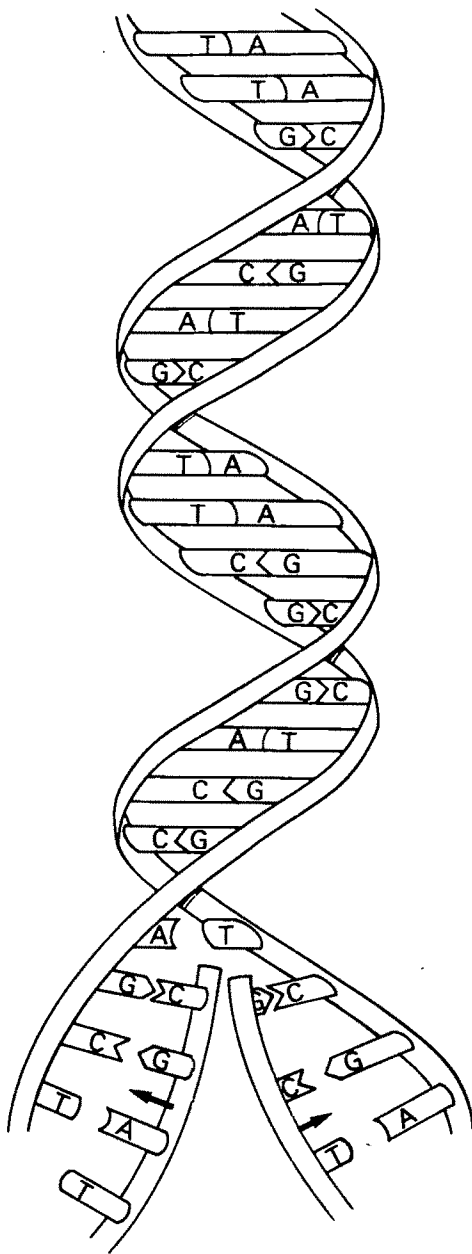


FIG. 1. The DNA double helix. The DNA strands can separate to allow replication.

unwind its two strands to allow one strand to serve as a template for the transcription of a base-pair-specific sequence of RNA. RNA is transported from the nucleus to the cytoplasm of the cell where translation of the RNA sequence into proteins occurs. The study of DNA can be directed at the DNA in the nucleus or its messenger product, RNA. We can study genes (DNA) or their expression (RNA).³⁻⁶

To study DNA it must first be extracted from a cell culture or tumor tissue sample. Extraction of nucleic acids is usually accomplished by lysis of cells with detergents and digestion of proteins with nonspecific proteases. Second chloroform and phenol are used to remove remaining lipids and proteins. Ethanol is added in the presence of an elevated salt concentration (100 to 500 mmol/L [millimolar]) to precipitate the DNA. Although these procedures result in chromosomal breaks, long enough pieces of DNA remain (about 70,000 base pairs) such that the entire lengths of most functioning gene sequences remain intact.⁷⁻¹⁰

After extraction DNA is treated with a restriction enzyme. Restriction enzymes, which were discovered in bacteria, cleave DNA in a highly specific fashion. Each restriction enzyme (of the more than 100 known) recognizes a unique sequence of DNA base pairs and cleaves the DNA only at sites containing this sequence. DNA treated with a restriction enzyme is cut into many fragments corresponding to the number of times the restriction enzyme's recognition sequence occurs (Fig. 2). The crucial point in this process is that restriction enzymes recognize specific short (4 to 8) nucleotide base-pair sequences. Therefore the DNA from many cells treated with a restriction enzyme will be cut into many fragments, all of identical size and sequence. For example, suppose we are interested in studying a gene that exists between point A and point B on a chromosome. A restriction enzyme can be selected that will specifically cut DNA at or near points A and B. If 100,000 cells are in the original sample, then nearly 100,000 copies of the gene or gene fragment will result from restriction enzyme cleavage. Because the restriction enzyme cuts specifically at points A and B, all 100,000 gene copies should have the same sequence and same length.⁷⁻¹⁰

After restriction enzyme digestion, gel electrophoresis is used to separate DNA fragments (Fig. 3). Agarose (usually at 0.5% to 1.0% solution) is mixed with ethidium bromide. Ethidium bromide fluoresces under ultraviolet light. Because it stereospecifically intercalates with the spiral groove of the DNA helix, ethidium bromide can be used as an indicator for the presence of DNA on a gel. The heated ethidium bromide and agarose solution is cast into a mini (50 mL), midi (150 mL), or large (500 mL) gel tray and is hardened at 4 C. A gel comb is used to create uniformly spaced wells across the width of the gel.

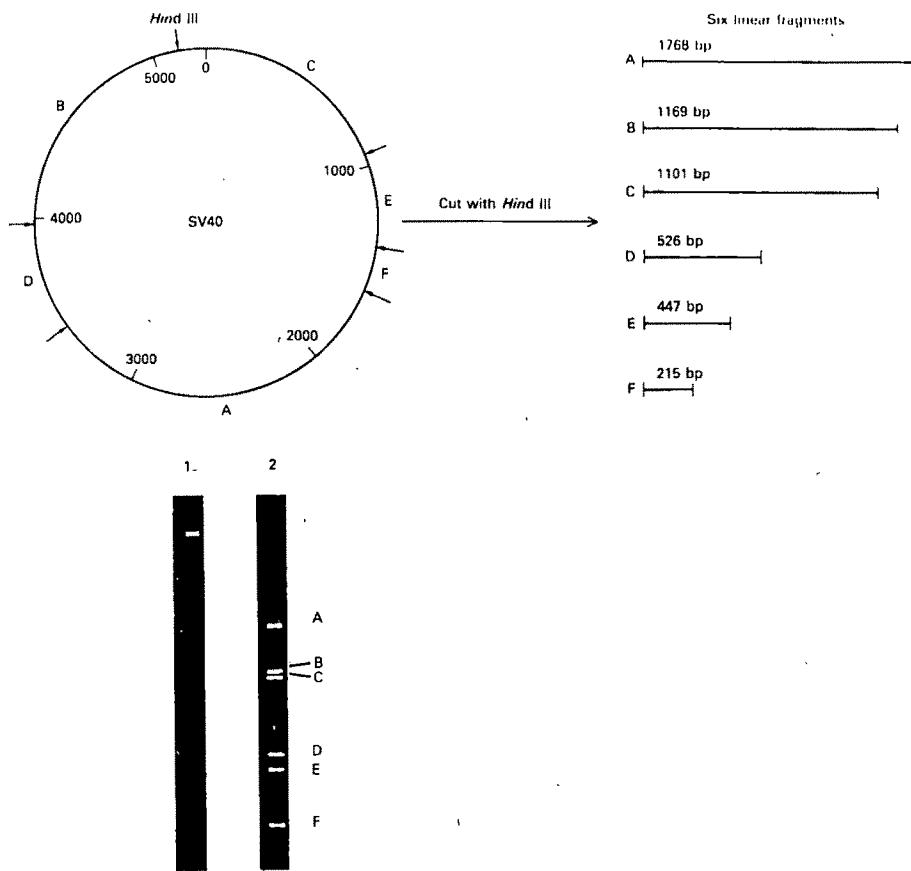


FIG. 2. Treatment of the virus SV40 DNA with the restriction enzyme *Hind*III results in six DNA fragments. Gel electrophoresis of uncut SV40 DNA results in one large, slowly migrating band (1), whereas treatment with *Hind*III results in six fragments (2) that migrate in the gel in inverse proportion to their length. From Darnell J, Lodish H, Baltimore D. Examining the sequences of nucleic acids and proteins. In *Molecular Cell Biology*. New York: WH Freeman and Co., 1986, p. 247 (Permission granted from the publisher).

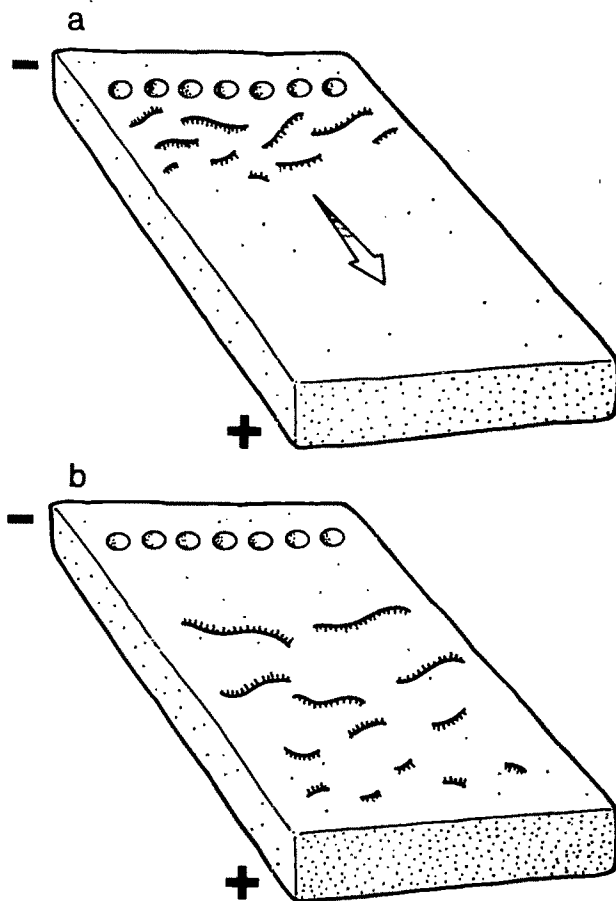
The sample of DNA is placed into the wells along with appropriate standards (DNA of known length). A charge (5 volts per 1 cm of gel length) is applied across the gel and the charged DNA molecules will migrate. Because of the negative charge on the phosphate backbone of DNA, the DNA fragments will move in a straight line toward the positive electrode, creating a tract called a lane. Fragments of all sizes have the same charge-to-mass ratio, so the only factor determining the rate of migration of a DNA fragment through the gel is its length. Suppose there are many gene fragments (500 base pairs long) after DNA extraction and restriction enzyme cutting. If the gel is illuminated under ultraviolet light there will be a discrete fluorescing band of DNA detected at a distance from its original start point corresponding to a DNA standard size 500 base pairs long. Other bands representing other DNA fragment lengths will also be visible.^{5,7-10}

For example, if the DNA is extracted from a sample of pure SV40 virus particles and cut with a restriction enzyme called *HIND* III, the DNA will be cut into six fragments because the SV40 virus DNA contains six sites with the sequence recognized by this restriction enzyme (Fig. 2). If a gel is run with the uncut SV40 DNA one large, slowly migrating band will be seen under ultraviolet light. If the DNA is cut with *HIND* III, however, six faster

migrating (smaller) fragments of DNA will be seen under ultraviolet light as six discrete bands.⁶

Southern and Northern Blotting

Southern blotting (Fig. 4), derived from the name of its inventor, E. M. Southern, is the name given to the process of transferring the product of gel electrophoresis onto a piece of nylon or nitrocellulose filter paper.^{5,7-10} Before blotting the DNA in the gel is rendered single stranded or is denatured by soaking the gel in sodium hydroxide. Therefore the DNA is transferred to the filter in a single-stranded form. Nylon is less brittle than nitrocellulose and so has gained favor. The transfer is accomplished by sandwiching the gel next to a piece of nylon filter. By either suction or capillary action, a buffer solution is pulled uniformly through the gel at right angles to the plane of the gel using absorbent paper. The flow of buffer from the gel toward the filter paper transfers the DNA (or RNA in which case the procedure is called Northern blotting) to the filter. The DNA is bound to the nylon by covalently crosslinking the phosphate backbone of the DNA to the nylon using ultraviolet light and baking in a vacuum oven. Because the DNA backbone had been crosslinked to the filter, single-stranded DNA will remain



FIGS. 3A and B. Gel electrophoresis. DNA fragments separate according to size. After DNA is placed into a well on one side of the gel (a) the fragments migrate. Shorter fragments move farther than larger fragments in an electric field (b). Standard DNA fragments of known length, such as *Hind*III cut SV40 DNA, can be used as a measuring stick for fragment size.

on the filter in the same pattern of sizes as on the gel slab. The nucleotide bases of the single-stranded DNA on the filter are in this way exposed so that a so-called DNA probe can be used to determine whether a specific sequence of DNA is on the filter.⁷⁻¹⁰

DNA Probes

After extraction, restriction enzyme cutting, gel electrophoresis, and blotting, the fragments of DNA derived from an entire genome are arranged by size on the nylon filter. The desired specific gene sequence can be found by using a segment of DNA called a probe. Use of probes takes advantage of single-stranded DNA's tendency to bind with or hybridize to a complementary single-stranded DNA segment. Probe use also depends on two physical properties of complementary DNA binding called cooperativity and stringency. DNA strand binding is said to be cooperative because the longer and more precisely matched two segments of DNA, the greater the thermal energy needed to separate them. Higher temperatures are required to separate longer segments of complementary DNA compared to shorter, less perfectly matched segments. A probe of 100 base pairs tends to remain bound to complementary DNA (cDNA) at temperatures that would cause denaturing of shorter segments or less perfect matches. If the probe used is an exact base-pair match to the sought for gene, then binding will occur at higher temperatures only to that gene's DNA on the filter paper.⁷⁻¹⁰

Oligonucleotide (relative short DNA segments) probes can be obtained commercially and are designed to be a perfect base-pair match to a segment of the gene of interest. The probe is labeled with P^{32} . The nylon sheet is placed

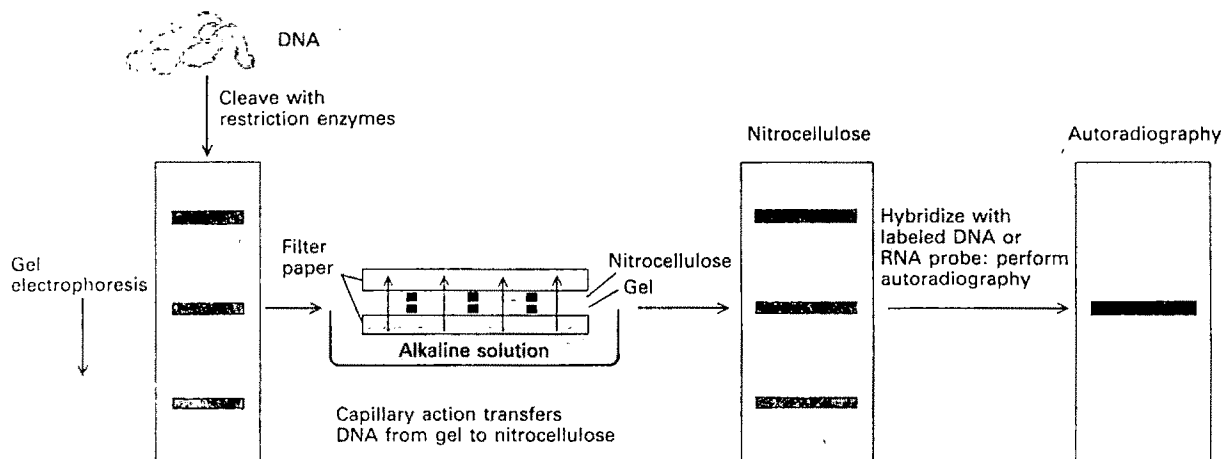


FIG. 4. Southern blotting. DNA cleaved into various lengths by a restriction enzyme is gel electrophoresed. The gel is treated by alkaline washing to render the DNA single stranded. A buffer is pulled through the gel so that the DNA strands migrate to the nylon filter. Radiolabeled shorter DNA fragments called probes are used to search for a segment of DNA on the filter paper. A positive result occurs when the labeled DNA, bound to complementary DNA on the filter, appears on an autoradiograph. From Darnell J, Lodish H, Baltimore D. Examining the sequences of nucleic acids and proteins. In *Molecular Cell Biology*. New York: WH Freeman and Co., 1986, p. 249 (Permission granted from the publisher).

in a solution with the probe at a temperature resulting in maximum stringency; that is, the conditions that maximize specific DNA binding and minimize nonspecific binding of shorter or imperfectly matched DNA segments. Hybridizing at 60 C, for example, is a more stringent condition than 37 C. If the probe is appropriately designed and the hybridizing reaction is performed at the optimal level of stringency, then the probe will bind only to the gene of interest with an exactly complementary DNA sequence on the filter. The filter paper now containing the probe hybridized to the gene under study is placed into a film cassette at -70°C . At this temperature, silver bromide crystals on the x-ray film are activated. When the film is developed, areas of the filter where specific probe to DNA binding occurred will show up as a dark band. This film exposure process is called autoradiography.⁷ The specificity of the result can be determined by the specificity of the probe and the conditions (temperature) at which the hybridization is performed. Using these methods, one gene within thousands of other genes can be located. So gels characterize DNA fragments by size. Hybridized blots characterize DNA fragments by exact DNA base-pair sequence. After one probe is used on the electrophoretic blot, that probe can be removed from the nylon with hot alkaline washes, leaving the single-stranded DNA behind. Then another probe, to another gene of interest, can be hybridized to the filter.⁷⁻¹⁰

DNA or RNA probes can be used to address simple questions. For example given a piece of tissue, suppose we want to know if the *myc* oncogene is present. Because the sequence of the *myc* gene is known, a probe for *myc* can be designed, purchased, and labeled with P^{32} . After DNA extraction, gel electrophoresis, and blotting, specific probe hybridization appearing on an autoradiograph as a dark spot would indicate that the gene or DNA segment is present in the tissue sample. Extracting the cell's mRNA and using, instead, an RNA probe not only can determine the presence of a gene but an estimate of its activity or expression into mRNA product can be made. That is we can take advantage of a probe's specificity to the DNA or RNA, to which it is complementary. Probes give answers to these questions: Is a gene present? How much of the gene is present? Is the gene's expression enhanced?

Clinical Applications

Finding An Oncogene (Focus Formation, Transfection, and Transformation)

How can these basic techniques be used to identify one cancer-causing gene within a sample of tissue? The first step is to develop an assay system for tumorigenicity. This is provided by cultured cells, typically the National Institutes of Health mouse 3T3 cell line. 3T3 cells in culture grow in uniform monolayers because their growth is regulated by a property called contact inhibition. When a

transforming cancer gene (oncogene) is introduced into the 3T3 cells in culture, the cells lose their contact inhibition and pile on each other to form a visible focus (called focus formation) (Fig. 5). Introducing human tumor tissue DNA into mouse cell culture is done by a process called transfection. DNA from a sample of human tumor tissue is isolated and added directly to a culture flask of mouse 3T3 cells as part of a calcium phosphate precipitate. Surprisingly the mouse 3T3 cells will take up, incorporate, and express the human DNA. 3T3 cells that have lost their growth regulation by this DNA transfection process are said to be transformed. The oncogene in the DNA

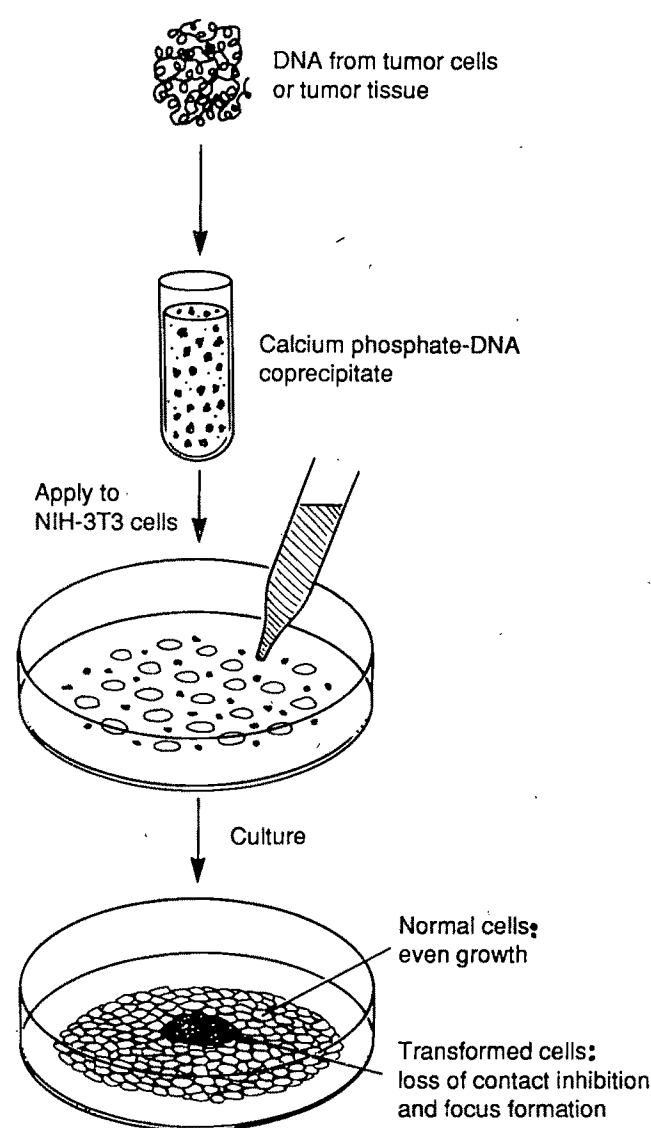


FIG. 5. Transfection of mouse NIH/3T3 cell culture as part of a calcium/phosphate precipitate. This process, called transfection, results in the uptake, incorporation, and expression of the tumor cell DNA. This will, in some cultures, result in the cell culture equivalent to a tumor called focus formation. By taking cells from the focus of transformed cells and repeating the transfection process, many cells that contain an oncogene can be grown in cell culture.

that has been spread over thousands of cells in a culture will betray itself by causing cell transformation. This will result in visible focus formation, analogous to a miniature tumor. By taking a sample of cells from the focus of transformed cells and repeating the transfection procedure, many transformed cells can be grown in cell culture. These transformed cells can then be injected into nude mice. Hard tumor formation is the evidence of the presence and expression of a cancer-causing gene.^{5,7-10}

Growing the transformed cells in culture provides a quantity of DNA sufficient for isolation and study. The DNA can be isolated from these cells and cut into fragments with restriction enzymes. Somewhere among these fragments from the transformed cells there may be a sequence of human DNA that can cause cancer. The task then remains to find it and identify its sequence. Locating the gene that transformed the cells can be accomplished by using phage lambda virus as a Trojan horse. This virus consists of a virus coat and single piece of DNA. The two ends of the viral DNA (called the arms) are the only DNA necessary for replication. The middle phage DNA portion, called the 'stuffer' region, can be replaced with another DNA sequence by cutting the arms with restriction enzymes and inserting the DNA from tumor cells. This is accomplished by mixing phage DNA with the stuffer region cut out with DNA isolated from tumor cells. In some phages the cancer-causing segment of DNA will be incorporated into the stuffer region with the help of ligase enzymes. These viruses can be spread over a lawn of bacteria (Fig. 6). In 6 hours many virus colonies will have caused visible areas of lysis in the bacterial lawn. Several of the viral colonies may be derived from viruses that have the human cancer gene incorporated into the stuffer region. The final step takes advantage of a unique feature of human DNA. It contains a specific sequence of 300 base pairs, called the ALU sequence, which is repeated many thousands of times in the human genome.^{5,7-10}

A template of the viral colonies on the bacterial lawn is created by touching a nylon filter to the phage-infected lawn (Fig. 6). The nylon filter adsorbs the intact virus particles. The protein of the phage coats can be lysed with detergents, and the DNA is then rendered single stranded by alkaline washing. A probe specific for the ALU sequence labeled with P^{32} can be hybridized to the nylon sheet and an autoradiograph is made. The one or several phage colonies that contain the human cancer gene detected by its contained ALU sequences will be identified as one or several dark spots on the x-ray film. Because the phage-infected bacterial lawn was originally transferred directly to the filter in mirror image, the phage colony containing the gene can be identified and grown in abundance by repeat culturing. Then by isolating the DNA fragments from the phage DNA and treating the phage DNA with a restriction enzyme to cut out the stuffer region, many copies of the cancer gene can be isolated. The

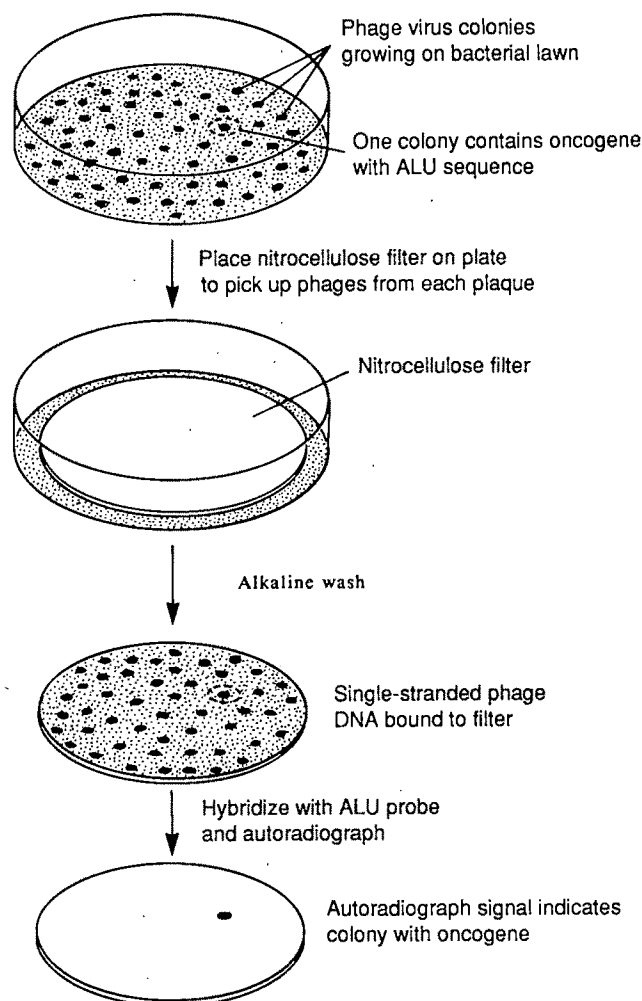


FIG. 6. The phage virus is used to isolate a human oncogene. After mouse NIH/3T3 cells transformed by human oncogene DNA are grown in quantity, their isolated DNA can be incorporated into a phage virus. However only one or several of hundreds or thousands of viral colonies will contain the intact oncogene in addition to the ALU sequence, the repeating DNA base-pair sequence unique to human DNA. After the viral DNA is transferred to the nylon filter, a radiolabeled probe complementary to the ALU sequence can be used to locate the one viral colony that contains a human gene.

ability of this DNA to transform culture cells and cause hard tumor formation can be reconfirmed after repeat transfection of 3T3 cells. Finally the exact base-pair sequence of the gene can be determined.¹¹ This process, which starts with only a piece of human tumor, can thus exploit recombinant DNA techniques to allow identification, isolation, and exact sequencing of the oncogene that actually converted a normal phenotype to a cancerous phenotype.

Polymerase Chain Reaction

It is impractical to apply these techniques to clinical medicine now because they might take a dozen workers many months to perform. Advancing DNA research technology, however, may change this situation. For ex-

ample the polymerase chain reaction (PCR) allows rapid amplification of the quantity of a specific DNA sequence from a tissue sample in a matter of hours.¹² The sensitivity of the procedure is so great that the DNA from one bacterium in 1 mL of water can be detected and a patient's tissue can be analyzed with only milligram-sized biopsy samples. The PCR is based on: (1) a bacterial DNA polymerase enzyme from the obligate thermophile bacterium *Thermus aquaticus*, which remains stable at 90 C, and (2) newly developed thermal cycling machines that can be programmed to repeat cycles of multiple temperatures between 0 C and 100 C. Suppose, for example, that only two copies of a specific gene with a known DNA sequence are present in a tissue sample. By designing appropriate short segments of DNA with sequences complementary to the ends of a segment of this known sequence, primers can be furnished that will allow a DNA polymerase to make copies of each strand of this known segment. By then adding enough free nucleotides as building blocks, and the *T. aquaticus* DNA polymerase, a reaction sequence can be started to amplify exponentially the number of copies of the desired gene. Using a thermal cycler, the reaction mixture is first heated to 90 C to separate all DNA into single strands. Second, the cycler cools the reaction to 46 C to allow the primers (one complementary to each end of the gene sequence being studied) to combine in sequence-specific fashion with the two gene copies. Third, the reaction mixture is heated to 70 C, the optimal temperature for the *T. aquaticus* DNA polymerase. The polymerase uses the DNA primers and the free nucleotides to make two segments of DNA, each complementary to the original two DNA segments. When the machine heats the reaction to 90 C again, all the strands separate. After the machine cycles 30 times, which only takes a few hours, the number of copies of the original two genes will be 2^{30} ! The PCR technology allows a specific gene to be amplified from the DNA of an extremely small tissue sample. The amplified DNA can be run on a gel, blotted, and hybridized to the probe specific for the DNA segment of interest.

The PCR also can be used to study expression of genes by detecting the presence of messenger RNA. The viral enzyme reverse transcriptase (RT) makes DNA from an RNA template. Using RT before the PCR reaction with the presence of messenger RNA can be inferred from detection of its complementary DNA sequence. That is, the presence of an oncogene alone may not be as significant as the fact that it is expressed or is transcribed to generate an excessive amount of mRNA and protein.

Recent work¹³ has demonstrated that the PCR can identify the presence of the human immunodeficiency virus in human blood samples up to 3 years before a positive test for the antibody. The polymerase chain reaction had detected specific retroviral DNA sequences in patients with multiple sclerosis,¹⁴ and has amplified DNA segments from 13,000-year-old prehistoric fossils and 5000-year-old mummies.¹⁵ That is, because the polymerase chain

reaction dramatically amplifies a specific DNA (or RNA) segment it has been and will be used to achieve levels of accuracy and specificity heretofore unachievable in clinical medicine.

Proto-oncogenes and Anti-oncogenes

The definition of an oncogene is that of a gene which transforms cells, but a normally functioning oncogene does not cause cancer. This definition derived from studies of tumor causing viruses which identified viral tumor genes.^{16,17} Surprisingly these genes (or closely related genes) exist in normal vertebrate cells and are called proto-oncogenes.¹⁸ Closely related cancer associated genes have been grouped into gene families based on function, for example, the *ras* or *myc* oncogene families.^{16,17} However, oncogene appears in some ways to be a misnomer because oncogenes code for classes of regulatory proteins which are centrally involved in cellular growth regulation. These oncogene protein products have been classified into growth factors, growth factor receptors, and the so called G-proteins which are guanine nucleotide binding proteins located in the plasma membrane and involved in cyclic AMP messenger cascades. Oncogene products may affect the growth of cells by their actions in the nucleus or at the cell membrane. The platelet derived growth factor (PDGF) B chain, for example, is almost identical to the transforming protein product of the simian sarcoma virus (SSV). Antibodies to PDGF revert SSV transformed cells to normal phenotype. The SSV protein product has PDGF activity and acts *via* PDGF receptors.^{19,20} Based only on the limited number of observations so far, it seems that oncogenes are important for more than cancer. They seem capable of controlling normal cellular function and wound healing.

A classic example of the potential of oncogene research is the *ras* oncogene.¹⁶ As little as a single point mutation in this gene has accounted for a change in the structure of its coded regulatory protein. This results in unregulated cell growth *in vitro*. The *myc* oncogene has been studied in human neuroblastoma tumors (neuroblastoma *myc* gene). The degree of this gene's amplification (number of extra gene copies) in one study has proven to be a better predictor of disease free survival and tumor behavior than clinical stage of disease. For example, study of the N. *myc* oncogene in stage II tumors has predicted tumor growth and disease progression.^{21,22}

In contrast to tumor inducing, the retinoblastoma (RB) gene exemplifies the concept of a tumor-suppressing gene or anti-oncogene.²³⁻²⁵ In retinoblastomas, both copies of the RB gene are missing. In cells that do not have the RB gene protein product, growth regulation is lost. That is, the term anti-oncogene is meant to imply that the gene is normally present and it or its protein product plays a central role in the regulation of cell growth. Finding a gene which causes neoplasm by its presence is easier than

identifying a gene which causes a tumor by its absence. The RB anti-oncogene illustrates an important point: cell growth is under both positive and negative control. Oncogenes can provide both types of control. Oncogenes or gene deletions have also been detected in tissue from common human tumors including small cell lung,²⁶ breast,²⁷ and colon carcinomas.²⁸⁻³⁰ Single oncogene alterations, however, are often not sufficient to make cells cancerous. Often in these tumors, changes in more than one gene and more than one chromosome appear necessary for tumor growth.

Oncogenes and Non-neoplastic Disease

Although their discovery occurred because of cancer research, oncogenes and DNA research will be important in multiple diseases. Oncogenes and their expressed products (proteins) have been measured in human atherosclerotic lesions. In particular, human coronary artery atherosclerotic plaque DNA has been used to transform NIH 3T3 cells in culture.³¹ The transformed cells have induced solid tumors in nude mice. In contrast, these changes were not induced by transfection with DNA derived from normal coronary artery. These findings suggest that atherosclerotic plaque expresses an oncogene. The same genetic alterations which cause cancer may also account for the smooth muscle proliferation of atherosclerotic plaques! Elevations in the mRNA for platelet derived growth factor have also been found in human atherosclerotic lesions.³² In rat models of myocardial hypertrophy, there is increased expression of the *ras*, *fos*, and *myc* oncogenes.³³⁻³⁵ The pattern of oncogene expression is specific to the etiology of the cardiac hypertrophy. For instance, left ventricular pressure overload produces a different pattern of oncogene expression than thyroid induced cardiac hypertrophy.³⁴ These preliminary findings suggest that oncogenes are central regulators of cell function and may show altered expression in many categories of disease.

Is Synthetic DNA Therapy Possible?

The technology which allows rapid and automated determination of the presence of a base-pair sequence and level of expression of oncogenes is developing. The future of DNA research will involve designed DNA therapies based on knowledge of the DNA sequence alterations responsible for the cancer or disease. For example, recently³⁶ an oncogene *c-ras*-1 relating to the tumorigenicity and radiation resistance of the squamous carcinoma cell line SQ-20B has been identified. Transfection of these tumor cells in cell culture using *c-ras*-1 DNA in reverse (antisense) orientation contained within a DNA plasmid reduced both the tumor cells tumorigenicity and radiation resistance. That is, based on the knowledge of the DNA sequence which, in part, accounts for the cancerous phenotype, DNA of backwards direction was used to prevent the expression of that DNA sequence. The cells were not

killed. Their phenotype was altered toward normal. As another example consider the implications of DNA sequence specific inhibition of human immunodeficiency virus (HIV) expression and replication. Treatment of T cells infected with HIV in culture with an antisense segment of DNA made with phosphothioate oligodeoxynucleotides (altered DNA) prevented the expression of the viral gene *rev* protein product, which is essential for viral replication.³⁷ The RB gene has been introduced into osteosarcoma cells lacking the RB gene using a nonviral viral vector.³⁸ The addition of the RB gene to neoplastic cells suppresses their neoplastic expression in culture. It also suppresses the tumorigenic potential of these cells when injected into nude mice.³⁸ The extraordinary fact about these DNA engineering experiments is that they are designed with complete DNA sequence specificity. That is, the attack on the tumor cell is designed to make it a normal cell again rather than to kill it. The normal bystander cells remain unharmed.

Cloned Genes Can Produce Human Hormones

Genetic engineering laboratories have used recombinant DNA techniques to clone genes for the production of human hormones and proteins. Once the sequence of the gene to be cloned is determined, the gene's DNA can be spliced into a bacterial plasmid adjacent to a chosen promoter region. Promoter regions enhance the downstream transcription of sequences. Inserting the DNA next to a promoter region may enhance its expression into the desired protein product. Thus human DNA can be recombined (hence recombinant DNA) with the bacterial chromosomes. In this way bacteria can be 'trained' to make a human protein in therapeutically useful quantities.^{5,7-10} Human 'recombinant' erythropoietin promises to lower transfusion requirements in chronically anemic patients.^{39,40} Recombinant human cytokines (interferons, tumor necrosis factor, and the interleukins) have been used successfully in the treatment of some neoplasms, such as hairy cell leukemia.⁴¹⁻⁴³ Recombinant human insulin has reduced the development of immunologic resistance to beef and pork insulin.⁴⁴ Recombinant human growth hormone has improved the treatment of dwarfism.⁴⁵ Human tissue plasminogen activator is used to promote reperfusion of occluded coronary arteries in the setting of myocardial ischemia.⁴⁶ The astounding fact is that all these treatments occur using pure human protein. They are exact replicas of the naturally occurring human proteins. The basic science of DNA research has allowed these extraordinary improvements in the quality of health care.

Recombinant DNA Techniques Will Change Medical Therapy

DNA research techniques have increased our understanding of the cause of cancer and other diseases resulting

from altered cell growth and regulation. These techniques will broadly change medical therapies. The treatment of bowel obstruction may not change, but the treatment of cancer and atherosclerotic disease will. Understanding the recombinant DNA language will enhance our role in surgical treatment and permit us to contribute to the use of DNA sequence-specific therapies as they develop in the future.

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Vascular Access in Patients with Arterial Insufficiency

Construction of Proximal Bridge Fistulae Based on Inflow from Axillary Branch Arteries

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Patients with renal failure and underlying peripheral vascular disease pose a difficult management problem in establishing long-term angioaccess for chronic hemodialysis. This report summarizes our experience with five debilitated patients who developed acute upper extremity ischemia after forearm fistula construction corrected by fistula ligation. Successful angioaccess was achieved without ischemia recurrence by construction of proximal bridge fistulae with arterial inflow based on branch arteries of the axillary artery. The relatively small size of the branch vessel was the main factor in limiting fistula flow while permitting normal distal axillary artery flow. In four patients direct fistula flow measurements ranged from 200 mL per minute to 620 mL per minute. Axillary arterial flow distal to the fistula ranged from 120 to 200 mL per minute and did not significantly change after fistula construction or during temporary occlusion of the fistula. Four of the five patients continue to dialyze uneventfully from 4 to 8.5 months. One patient died after discontinuation of dialysis 1 month after operation.

THE UPPER EXTREMITY prosthetic interposition arteriovenous, or bridge graft fistula, is the most common and preferred long-term angioaccess whenever a primary Cimino-Brescia arteriovenous fistula (AVF) has failed or the fistula cannot be constructed for technical reasons.¹⁻³ Such an interposition fistula can be constructed between virtually any artery and vein of suitable size, leading to many possible graft configurations. In most circumstances, however, a few basic patterns will suffice. Sometimes patients with severe peripheral vascular disease (PVD), often associated with diabetes mellitus, are encountered who develop acute upper extremity ischemia subsequent to fistula placement. This problem generally manifests unexpectedly in the early postoperative period as a pale, cool, and continuously painful hand with associated diminished motor function and numb sensation. These symptoms may intensify during dialysis. Digital compression of the interposition graft, to restrict fistula

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flow or of the distal radial artery in the case of a primary AVF, may provide partial pain relief. The primary treatment goal is to promptly restore adequate flow to the distal arm and hand to prevent limb loss and preserve hand function.⁴ This generally requires ligation of the fistula. Banding of the bridge fistula has been reported but is not widely practiced due to inability to precisely restrict fistula flow, thereby restoring adequate distal extremity blood flow while preserving fistula patency. Construction of an arterial anastomosis small enough to limit fistula flow is, in our experience, not practical. Radial artery ligation to a primary AVF may worsen the ischemia. The problem of recurrent ischemia at a new access site still remains for these patients with severe PVD.

We report here our experience with five patients who developed upper extremity ischemia after construction of forearm AVF necessitating, in each case, fistula ligation to restore adequate extremity blood flow. Each patient underwent successful construction of a proximal bridge graft AVF based on arterial inflow from branch vessels of the axillary artery. This procedure might be described as a proximal axillary branch artery bridge graft fistula referred to here as simply a proximal fistula. This initial experience suggests that adequate fistula blood flow for hemodialysis can be safely accomplished without compromise to distal extremity blood flow in patients with severe PVD.

Patients and Methods

Between March and July 1989, five patients were encountered with underlying PVD who developed upper extremity ischemia subsequent to AVF construction for dialysis. In all cases the fistulae were ligated to correct the

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TABLE 1. *Vascular Risk Factors Identified in Five Patients Requiring Proximal Fistula Placement*

Patient	Age	Risk Factors
L.C.	61	Diabetes; recent subendocardial MI
D.J.	68	Diabetes; left below-knee amputation; femoral-femoral bypass
D.S.	77	Hypertension; congestive heart failure
E.W.	71	Diabetes; left below-knee amputation; recent antero-septal MI; gangrene right thumb and left index finger; ischemic hand after fistula placement 1 year ago
D.C.	69	Diabetes; ischemic hand after fistula placement 2 years ago

ischemia problem. Preoperative angiography was used to define arterial anatomy before proximal fistula construction. Intraoperative blood flow measurements were taken with a Transonics HT201DS flowmeter system (Transonics Systems Inc., Ithaca, NY) in the last four patients in this series. Direct flow measurements through Plasma Tetrafluoroethylene (PI-TFE) bridge grafts (Medtronic Inc., Minneapolis, MN) were validated in the laboratory by timed volume collection. Bridge fistulae were constructed with 6-mm nontapered grafts. Upper extremity arterial Doppler examinations were performed before and after surgery for comparison purposes. Preoperative arm venography was performed in all patients who had indwelling subclavian temporary dialysis catheters to identify presence of subclavian vein stenosis or occlusion, which would preclude adequate fistula outflow. Paired Student t test was used for analysis of blood flow data with p values less than 0.05 considered significant.

Case Report

Patient 1 is a 61-year-old diabetic woman with chronic renal insufficiency who sustained an acute subendocardial myocardial infarction complicated by congestive heart failure and acute renal failure. Dialysis was initiated via a right subclavian vein temporary dialysis catheter. Three weeks after infarction, the patient underwent construction of a left forearm PI-TFE loop bridge AV fistula with arterial inflow from the side of the distal brachial artery and venous outflow into the side of the median cubital vein. After operation she developed progressive hand pain and diminished motor function during the subsequent week. Doppler examination demonstrated blunted left radial and ulnar arterial waveforms with a digit-to-arm index (D/AI) of 0 and a contralateral D/AI of 0.38. A fistulogram revealed normal anastomoses, brisk fistula flow, and poor

distal arm antegrade blood flow. The interosseous artery was diffusely narrowed, the radial and ulnar arteries were occluded but reconstituted distally, the deep palmar arch was patent, and a mild stenosis of the brachial artery just proximal to the graft anastomosis was noted. The antecubital fossa incision was re-explored. With fistula occlusion the previously absent Doppler signal in the distal radial and ulnar arteries became detectable. Fistula blood flow was measured at 300 mL per minute and the brachial artery blood flow proximal to the patent fistula was measured at 350 mL per minute, leaving a calculated distal blood flow to this extremity of 50 mL per minute. There was no stenosis of the brachial artery. The fistula was removed and the brachial artery closed by patch angioplasty with subsequent blood flow measured at 360 mL per minute. After operation the patient's ischemic symptoms resolved. Doppler examination disclosed return of brisk arterial waveforms in the left radial and ulnar arteries and increment in the D/AI from 0 to 0.20. Venography demonstrated right subclavian vein stenosis due to an indwelling temporary dialysis catheter precluding fistula placement on the right. Left upper extremity angiography revealed mild irregularity of the proximal subclavian artery, a normal axillary artery with a 5-mm diameter subscapular artery branch, and a normal brachial artery. Under local anesthesia, the patient underwent construction of a left upper arm proximal bridge fistula using a PI-TFE conduit. Graft inflow was taken from the end of the subscapular artery and outflow into the side of the basilic vein just above the elbow. The graft was brought through a subcutaneous tunnel along the anterior aspect of the brachium and directed in a loop fashion just above the elbow for venous anastomosis. Intraoperative blood flow measurements demonstrated fistula flow of 402 mL per minute with distal axillary artery flow of 186 mL per minute before fistula placement and 172 mL per minute after fistula flow was established. After operation the patient's hand remained warm and pain free. Doppler examination showed normal brachial, radial, and ulnar arterial waveforms bilaterally with D/AI values unchanged from preoperative values. Dialysis was begun through the fistula 1 week after operation.

Patient Selection and Evaluation

All five cases involve patients who developed unexpected acute upper extremity ischemia associated with placement of a forearm bridge graft fistula. Risk factors for PVD evident in this group are listed in Table 1. Severe ischemia symptoms, of which intense hand pain is the hallmark, appeared in the early postoperative period in four patients and subacutely in patient 3. This patient initially manifested hand pain on dialysis, which progressed over a 4-week period to continuous pain. Fistula characteristics associated with extremity ischemia are shown in Table 2. Patient 2 underwent sequential construction and ligation of two fistulae in the left forearm. A Cimino-Brescia fistula was initially constructed that re-

TABLE 2. *Fistula Characteristics Associated with Extremity Ischemia*

Patient	Configuration	Arterial Inflow	Venous Outflow	Interval to Ligation	Resolution of Ischemia
L.C.	Left forearm loop PTFE	Brachial	Basilic	10 days	Yes
D.J.	Left Cimino-Brescia	Radial	Cephalic	48 hours	Yes
	Left forearm loop PTFE	Brachial	Median cubital	24 hours	Yes
D.S.	Left forearm loop PTFE	Brachial	Median cubital	4 weeks	Yes
E.W.	Left forearm loop PTFE	Brachial	Basilic	2 hours	Yes
D.C.	Right forearm loop PTFE	Brachial	Basilic	2 hours	Yes

TABLE 3. Digit/Arm (D/AI) and Forearm/Arm (F/AI) Indices Associated with Development of Hand Ischemia After Forearm Loop Fistula Placement Necessitating Fistula Ligation

Patient	With Patient Fistula		Following Fistula Ligation		Contralateral Extremity	
	D/AI	F/AI	D/AI	F/AI	D/AI	F/AI
L.C.	0	ND*	0.20	0.86	0.33	0.98
D.J.	0	ND*	0.78	0.94	0.76	0.92
D.S.	0	ND*	0.79	ND	0.86	1.0

ND, not done.

* Dampened arterial waveforms.

sulted in hand ischemia. Subsequent ipsilateral PTFE loop bridge fistula resulted in return of the hand ischemia. Fistula ligation was therapeutic in all cases.

Doppler studies performed on the first three patients in this series who developed extremity ischemia after forearm bridge fistula construction at this institution are shown in Table 3. In each case the ischemic extremity demonstrated a D/AI of zero and blunted forearm and digit arterial waveforms confirming the diagnosis of severe hand ischemia. After fistula ligation, these findings normalized to that of the contralateral extremity. D/AI or F/AI values were not retrospectively predictive for this complication. The last two patients in this series presented with a history of hand ischemia after fistula placement requiring ligation and prompting referral for proximal bridge fistula construction.

Surgical Approach to the Axillary Artery and Its Branches

With the arm abducted, the skin and subcutaneous tissue of the axilla is infiltrated with 0.5% xylocaine. A horizontal incision is made from the apex of the axilla to the proximal upper arm and the pectoralis major is retracted medially. The axillary artery is divided into three regions (Fig. 1). The first region spans from the first rib to pectoralis minor and gives rise to a small-caliber highest thoracic artery. The second region lies posterior to the pectoralis minor and gives rise to two relatively small branches: the thoracoacromial and lateral thoracic arteries. The third region lies between pectoralis minor and teres major and gives rise to three relatively large branches: the subscapular, the posterior circumflex humeral (PCH), and the anterior circumflex humeral (ACH) arteries. With judicious use of the cautery, supplemental xylocaine infiltration and avoidance of nerve manipulation, we found that exposure of the second and third regions of the axillary artery and its branches were well tolerated without general anesthesia, as was done in the latter four cases in this series. The distal axillary artery is localized by palpation and sharply dissected. The PCH artery is initially encountered arising from the posterior-inferior aspect of the axillary artery near the lateral boundary marked by teres major. The ACH artery is generally smaller and arises nearby from the posterior superior aspect of the axillary artery. Because dissection is performed proximally, the

subscapular artery generally arises from the inferior aspect of third portion of the axillary artery near the pectoralis minor. Anatomic variations can occur. Patient 4 possessed a small-caliber subscapular artery with aberrant origin from the first portion of the axillary artery, which was not accessible. In this case a 3.5-mm diameter PCH artery was used for fistula inflow. After mobilization and ligation of three small branches, the end of the PCH was anastomosed to the end of the P1-TFE graft. The thoracodorsal and circumflex scapular branches of the subscapular artery can be located by palpation below the axillary vein and nerve trunks or can be traced distally during mobilization of the subscapular artery. Patient 2 possessed a suitable thoracodorsal artery to support fistula flow. The end of the expanded polytetrafluoroethylene (PTFE) graft was anastomosed to the side of this vessel below the axillary vein and brachial plexus. In three patients the entire subscapular artery was mobilized and distal branches were ligated, thus allowing its transposition anterior to the ax-

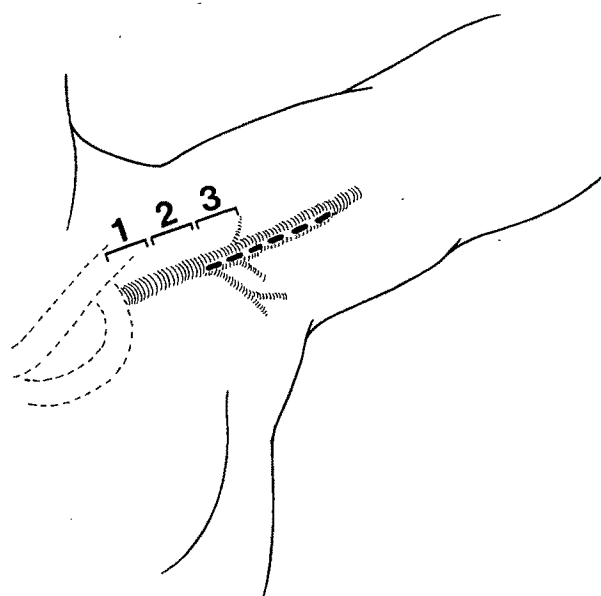
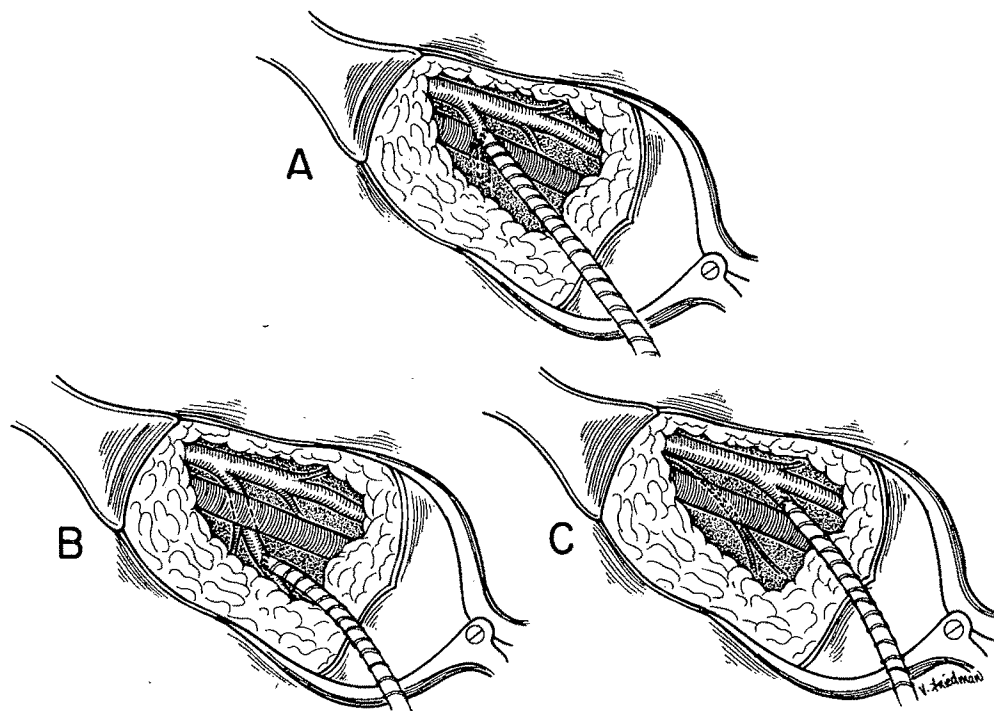


FIG. 1. Surgical approach to the third portion of the axillary artery and its major branches used for proximal bridge fistula arterial inflow. Anatomically the axillary artery is divided into three regions (1, 2, 3), of which the latter two are readily accessible via the illustrated transaxillary approach.



FIGS. 2A–C. Axillary view illustrating variations in fistula arterial inflow used in construction of the proximal bridge fistulae in this series. (A) The graft is anastomosed to the end of the subscapular artery; (B) the graft is anastomosed to the side of the thoracodorsal artery; and (C) the graft is anastomosed to the end of the posterior circumflex humeral artery. In C the subscapular artery was unsuitable due to its small caliber and aberrant origin.

illary vein to facilitate anastomosis. Variations in fistula arterial inflow are shown in Figure 2. In all cases vascular clamps were applied directly to the branch arteries used for fistula inflow during arterial anastomosis, making it unnecessary to occlude axillary artery flow. After arterial anastomosis the graft is directed through a tight subcutaneous tunnel with a Kelly-Wick access tunneler (Impra, Inc., Tempe, AZ) and venous anastomosis is performed to the side of a suitable-sized vein.

Results

The proximal fistula configurations used in the five patients of this series are listed in Table 4. Patients 1, 3, 4, and 5 underwent fistula placement into the ipsilateral extremity, which previously had developed ischemia asso-

ciated with a functioning forearm bridge fistula. This was necessary because of subclavian vein stenosis associated with temporary dialysis catheter placement documented by venography. No patient in this series developed extremity ischemia associated with proximal bridge fistula placement. D/AI and F/AI before and after proximal fistula construction remained unchanged, as shown in Table 5. These data also demonstrate comparable values in both upper extremities. Forearm Doppler waveforms for patient 3, who was representative of this group, are shown in Figure 3. The ischemic extremity (Fig. 3B), in comparison to the contralateral arm (Fig. 3A), demonstrates blunting of the brachial, radial, ulnar, and digit arterial waveforms. These waveforms normalized after fistula ligation (Fig. 3C) and remained so after proximal fistula construction (Fig. 3D).

TABLE 4. Proximal Fistula Construction After Ligation of the Ischemia-related Forearm Fistula

Patient	Configuration	Arterial Inflow	Venous Outflow	Ischemia Recurrence	Patency (Months)
L.C.	Ipsilateral Left upper arm loop PI-TFE	Subscapular	Basilic	No	6
D.J.	Contralateral Right forearm loop PTFE	Thoracodorsal	Median cubital	No	8.5
D.S.	Ipsilateral Left upper arm loop PI-TFE	Subscapular	Basilic	No	5.5
E.W.	Ipsilateral Left upper arm loop PI-TFE	Posterior Circumflex humoral	Basilic	No	1*
D.C.	Ipsilateral Right forearm loop PI-TFE	Subscapular	Cephalic	No	4

* Dialysis discontinued at 1 month.

TABLE 5. Digit/Arm and Forearm/Arm Indices Before and After Proximal Fistula Construction

Patient	Digit/Arm Index			Forearm/Arm Index		
	Preop	Postop	Contralateral	Preop	Postop	Contralateral
L.C.	0.20	0.23	0.31	0.86	0.69	0.88
D.J.	0.76	1.0	1.0	0.92	ND	0.94
D.S.	0.79	1.0	1.0	ND	ND	ND
E.W.	0.21	0.33	0.20	>1	1.0	1.0
D.C.	0.70	0.69	0.84	1.0	1.0	1.0

ND, not done.

Blood flow through the proximal P1-TFE fistula and the distal axillary artery was measured during operation in patients 1, 3, 4, and 5, as shown in Table 6. In all cases fistula flow was sufficient. There was no significant change in distal axillary artery flow after proximal fistula construction or during temporary fistula occlusion. Postoperative fistulograms were obtained at 2 months. Arterial segment detail views are shown in Figure 4 for patients 2 and 5, in whom arterial inflow was taken from the thoracodorsal and subscapular arteries, respectively. Patient 4 did not have a fistulogram performed because dialysis was discontinued at 1 month when she sustained cerebral anoxic damage after three successive and profound hypotensive episodes. This fistula thrombosed during the third hypotensive episode. The four remaining patients continue to dialyze efficiently through the proximal bridge fistulae with a mean follow-up period of 6 months (Table 4).

Discussion

Severe vascular insufficiency after placement of permanent vascular access for hemodialysis can result in loss of limb or permanent functional impairment if not

promptly corrected.⁴⁻⁶ Usually construction of lower extremity fistulae is not considered in patients with advanced age, history of significant vascular disease, or long-standing diabetes because of this potential problem. The upper extremity fistula is preferred because attendant risks for ischemic complications are less. Extremity ischemia results from excessive shunting of blood through the low-resistance 'venous sink' or from retrograde flow in the artery distal to the fistula or both.⁷⁻¹⁰ This phenomenon is best described in the side-to-side distal radiocephalic fistula in which blood from the ulnar artery and collaterals is shunted across the hand *via* the superficial and deep palmar arches to connect with the distal branches of the radial artery. Ischemia may be remedied by ligation of the radial artery distal to the fistula with preservation of fistula flow. However, in patients with severe PVD, arterial ligation may be detrimental to hand perfusion due to inadequate antegrade blood flow and poor collateral circulation into diseased distal vessels. Ligation prevents reconstruction of prefistula blood flow status. Although banding of the bridge fistula has been reported for management of vascular steal, it is seldom used because satisfactory reduction of fistula flow to a level that restores distal arm and hand perfusion without resulting in fistula thrombosis is unreliable.¹⁰⁻¹² The primary goal in man-

FIGS. 3A-D. Forearm Doppler arterial waveforms obtained in patient 3. There is marked blunting of forearm and digit arterial waveforms associated with a patent left loop bridge fistula (B) resulting in hand ischemia as compared to the contralateral extremity (A). Waveforms normalized after fistula ligation (C) and remained so after ipsilateral proximal bridge fistula construction (D).

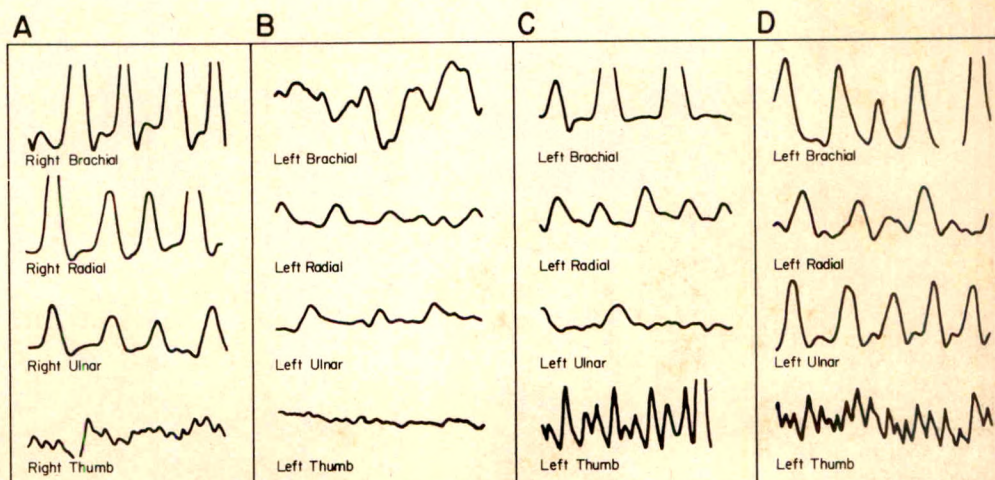


TABLE 6. Intraoperative Blood Flow Measurements During Proximal Fistula Construction

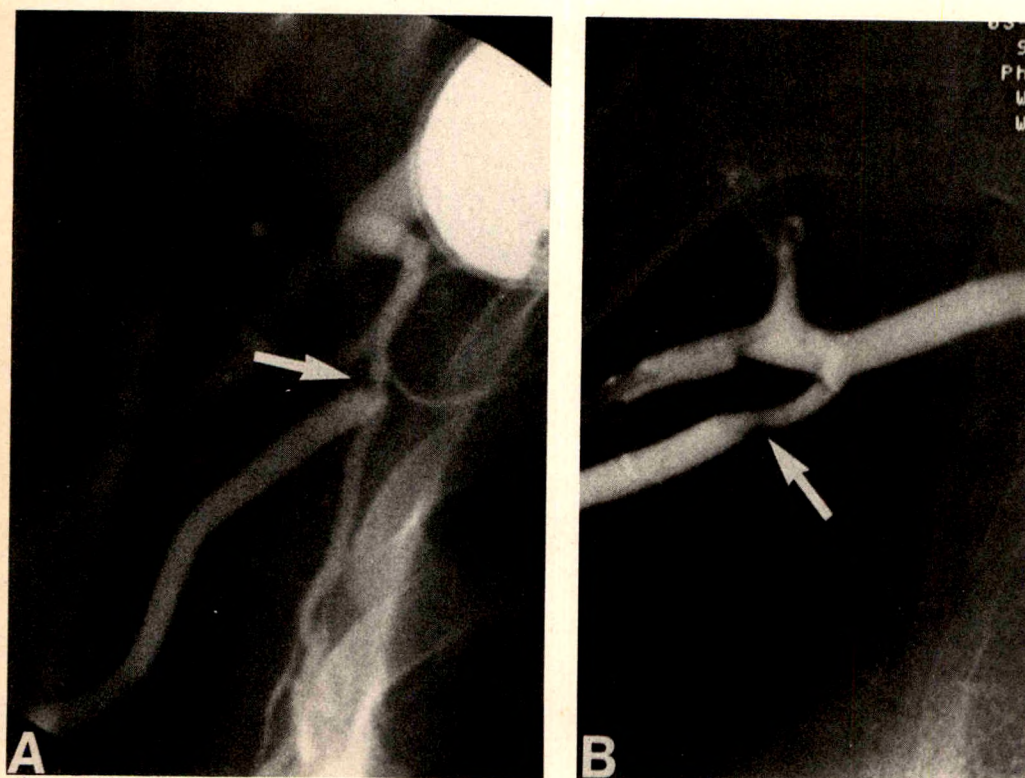
Patient	Arterial Inflow	Fistula Flow (mL/min)	Axillary Artery Flow (mL/min)		
			Before Fistula	With Open Fistula*	With Fistula Occlusion*
L.C.	Subscapular	402	186	172	175
D.S.	Subscapular	620	160	148	150
E.W.	Posterior circumflex humoral	220	200	200	200
D.C.	Subscapular	475	120	115	115

* p = NS compared to axillary artery flow before fistula construction.

agement of an ischemia complication is to restore extremity blood flow, even at the cost of sacrificing the fistula. This leaves the surgeon with the dilemma of adequate access placement while avoiding distal ischemia. Fistula construction at an alternate site carries significant risk for recurrent limb ischemia, as occurred with patient 2. Use of a small-diameter graft and/or tailoring of the arterial anastomoses to limit fistula flow are poor solutions.¹³ Small-diameter grafts provide difficult targets for dialysis personnel to cannulate. Significant restriction of fistula blood flow precludes efficient dialysis and increases the chance for thrombosis. Importantly it is almost technically impossible to construct a suitably small arterial anastomosis that permits adequate fistula and distal arterial flow.¹⁴ As illustrated by patient 1, extremity ischemia can occur with even a modest fistula blood flow. Venous dialysis catheters provide only a short-term access solution.

Renal transplantation and peritoneal dialysis as alternatives to hemodialysis often are not applicable because of medical contraindications.

We hypothesized that arterial inflow into a fistula from a small branch artery arising from the proximal arterial tree may allow sufficient fistula blood flow to permit efficient dialysis without compromise to extremity blood flow. The limiting factor to fistula flow would be the small size of the branch vessel from a large main trunk. This would circumvent the need to construct a technically difficult small anastomosis. For patient 2, the fistula was constructed with an arterial anastomosis to the side of the thoracodorsal artery. In patients 1, 3, and 5, arterial anatomy dictated that fistula arterial inflow originates from the end of the subscapular artery. In patient 4, the subscapular artery was of small caliber arising from the first portion of the axillary artery, and therefore a relatively



FIGS. 4A and B. Postoperative fistulogram arterial anastomotic (arrow) detail views. (A) To the side of the thoracodorsal artery for patient 2. (B) To the end of the subscapular artery for patient 5. Brisk fistula and arterial flow was demonstrated in each of the four patients studied.

large-caliber PCH artery was used to provide adequate arterial inflow. Any suitable-caliber (more than 3 mm) branch artery of the axillary artery appears to provide adequate fistula flow without jeopardizing distal arm flow. Surgery can be readily performed under local anesthesia with mild sedation. Preoperative arteriography has proved helpful in proper planning of the fistula by delineating arterial anatomy and relevant atherosclerotic disease. In all five cases the proximal arm vasculature was relatively normal, despite severe distal disease. Use of the P1-TFE graft has allowed direct fistula blood flow measurement, which is not possible with expanded polymer grafts such as PTFE.

Identification of patients who will develop an ischemic extremity associated with fistula placement remains elusive. Clinical examination, including the Allen's test, digit and forearm pressures, and Doppler ultrasound waveform analysis, was not helpful in our experience. Prompt recognition of ischemia, however, is critical to proper management. Doppler studies are useful for confirmation of the diagnosis as well as monitoring outcome after fistula ligation. Despite a previous episode of extremity ischemia related to a patent fistula, recurrence of this problem was not seen in any of our patients after proximal fistula construction based on inflow from branches of the axillary artery. In fact four of these patients successfully underwent proximal fistula placement into the ipsilateral arm.

From this experience it appears that arterial insufficiency following standard fistula placement does not preclude successful vascular access. The proximal bridge fistula, as we have described, can provide adequate blood flow to maintain efficient dialysis without recurrence of extremity ischemia and thus should be a useful addition to the armamentarium of the vascular-access surgeon.

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Long-term Follow-up of Brachial Artery Ligation in Children

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Ligation of the brachial artery in the antecubital fossa in children can be performed without limb loss, but the effect on subsequent limb growth is unknown. From 1969 to 1974, brachial artery ligation for insertion of a Scribner shunt was performed in 27 patients with a mean age of 8.4 years (range, 3 to 15 years). We examined 11 patients, all with functional renal transplants, a mean of 15.8 years (range, 13 to 18 years) after ligation. Nine patients had unilateral ligation and two had bilateral ligation. The patients were examined for arm length and circumference, resting blood pressure at the wrist, neurologic function of the arm, and exercise tolerance. A significant difference in resting arterial pressures in the ligated extremity was uniformly noted (mean systolic pressure 106 mmHg *versus* 123 mmHg in 7 patients, $p < 0.01$). Although no patient specifically complained of problems with the ligated side, six of nine patients with unilateral ligation experienced arm discomfort on stress testing. There was no significant difference in limb circumference or length between the ligated and unligated extremity. Ligation of the brachial artery in growing children with renal disease caused diminished resting pressure and mildly decreased exercise tolerance but did not lead to limb loss or subsequent growth abnormalities.

BRACHIAL ARTERY LIGATION for the treatment of traumatic injuries carries a significant risk of gangrene. DeBakey and Simeone¹ reported an amputation rate of 26% with brachial artery injury during WW II. However these patients had multiple associated injuries, including venous and nerve injuries. The location of occlusion of the brachial artery is also important because there is a known incidence of thrombosis of the brachial artery in the antecubital fossa after cardiac catheterization as high as 10%, usually without limb loss.^{2,3} These patients do not develop gangrene of the arm, but

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some will have symptoms of arm ischemia with exercise.⁴⁻⁶ Because the incidence of exercise-induced ischemia is so high, ligation of the brachial artery in childhood could potentially have adverse effects on limb growth. Indeed several authors have documented impaired limb growth of the leg after femoral artery occlusion in children.⁷⁻⁹

Widespread availability of hemodialysis in the 1960s led to an increased need for vascular access for dialysis. This was more problematic in children due to their small vessels. From 1969 to 1974, the distal third of the brachial artery was routinely used for Scribner shunt insertion at the Childrens Hospital of Los Angeles when the radial artery was too small. The brachial artery was ligated during the procedure. The purpose of this study was to evaluate the long-term effects of brachial artery ligation in childhood on subsequent limb growth and function.

Methods

The hospital records of all patients undergoing upper-extremity vascular access procedures from 1967 to 1974 at the Childrens Hospital of Los Angeles were reviewed. Operative records were reviewed and only those patients who underwent brachial artery ligation were included in the study. Individual surgeon's office records and dialysis records were reviewed for any intra- or postoperative complications. Attempts were made to contact all living patients residing in the southern California area.

Those patients who were contacted and agreed to par-

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ticipate were all examined by one individual (CF). Patients were questioned about handedness, any subsequent trauma to the extremities, and symptoms of pain, numbness, paresthesia, weakness, or skin color change. Evaluation of both extremities included a neurologic examination, motor function examination, and length measurements. Measurements of length were taken from bony prominences and included from the acromion to the middle finger tip and lateral epicondyle and from the medial epicondyle to the medial styloid and the middle finger tip. Arm, forearm, and wrist circumference were also measured. Resting doppler blood pressures in the radial and ulnar arteries were recorded in both arms. The patients were asked to squeeze a rubber ball 60 times per minute for 2 minutes. Any symptoms or physical changes were noted.

The data between both arms were analyzed using the paired, two-tailed *t* test. Significance was assumed when a *p* value of less than 0.05 was achieved.

Results

A total of 104 patients had an upper extremity Scribner shunt placed from 1969 to 1974. Forty of these patients were known to have died. Of the remaining 64 patients, 27 received a brachial artery Scribner shunt. We contacted 11 of these patients. The remaining patients were lost to follow-up or lived in another state. The mean age at the time of brachial artery ligation was 8.4 years, with a range of 3 to 15 years. The patients were examined at a mean of 15.8 years (range, 13 to 18 years) after ligation. All patients had functioning renal transplants at the time of the examination.

No patient in the series had episodes of immediate limb ischemia or limb loss at the time of shunt insertion. Two of the eleven evaluable patients had received bilateral brachial artery shunts and are therefore not included in the comparisons between sides. In five patients the brachial artery of the dominant hand was ligated, and in four patients the brachial artery of the nondominant hand was ligated.

As outlined in Table 1, there was no significant difference in any measurement of arm length or arm circumference between the ligated and unligated extremities. There were also no abnormalities in the motor or neurologic examination between sides.

Seven patients were evaluated for blood pressure comparison between the ligated and unligated extremity (one patient refused and the other had a functioning upper arm Gortex fistula). There was a significant difference (*p* < 0.01) in resting arterial pressures between the ligated (106 mmHg) and unligated (123 mmHg) arms. Although no patient specifically complained of problems, six of the nine patients with unilateral ligation experienced arm discomfort or paresthesia in the ligated arm with exercise.

Discussion

Occlusion of the femoral artery in children after catheterization has been shown to interfere with subsequent growth of the leg.^{7,8} Interruption of the subclavian artery for the creation of a Blalock-Taussig shunt also has been shown to impede arm growth.^{10,11} We were concerned that ligation of the brachial artery in growing children would also affect forearm growth. This does not appear to occur, however, and there are several possible explanations. The brachial artery has several well-formed collaterals, including the profunda brachii, and it is probable that these vessels supply sufficient flow for limb growth in children with chronic renal failure. Children with renal failure have impaired growth and the overall retarded growth may make differences more difficult to detect. Steroids also can cause growth failure and most of these patients received steroids for immunosuppression. Most forearm growth is completed by age 12 years.¹² While the mean age of our patients was 8.4 years, it is probable that most had completed more than one half of the ultimate forearm growth so that subtle changes could be difficult to detect.

Brachial artery occlusion after cardiac catheterization rarely leads to limb loss, probably due to the rich collateral network around the elbow. Although there is rarely limb-threatening ischemia with occlusion at the elbow, chronic arterial insufficiency is well described.^{13,14} None of the patients in this series complained of symptoms with direct questioning, but six of the nine with unilateral ligation had some symptoms induced by exercise. The life-style of most of these patients does not require prolonged use of the arm, which is probably why they did not specifically complain of problems.

The brachial artery in children may be safely ligated in the antecubital fossa, if necessary. In a population of children with renal failure, this does not lead to altered growth of the forearm, although most patients develop exercise-induced symptoms in the ligated extremity.

TABLE 1. Arm Length and Circumference (Mean $\pm$ SD)

	Measurement	Ligated	Unligated
Length	ACR-MFT	61.2 $\pm$ 5.3	61.4 $\pm$ 4.7
	ACR-LE	25.9 $\pm$ 2.4	25.6 $\pm$ 2.2
	ME-MFT	37.1 $\pm$ 2.8	37.5 $\pm$ 2.5
	ME-MS	21.0 $\pm$ 1.5	21.6 $\pm$ 1.6
Circumference	Arm	25.4 $\pm$ 4.3	25.7 $\pm$ 3.9
	Forearm	22.3 $\pm$ 2.4	22.0 $\pm$ 2.2
	Wrist	14.3 $\pm$ 1.0	14.1 $\pm$ 1.2

ACR, acromion; MFT, middle finger tip; LE, lateral epicondyle; ME, medial epicondyle; MS, medial styloid.

All measurements were made in centimeters

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Shock, Transfusion, and Pneumonectomy

Death Is Due to Right Heart Failure and Increased Pulmonary Vascular Resistance

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To determine the physiologic cardiopulmonary abnormalities leading to death when pneumonectomy is required to stop bleeding in patients in hemorrhagic shock, we compared cardiopulmonary responses to resuscitation in pigs undergoing hemorrhagic shock alone, pneumonectomy alone, and hemorrhagic shock plus pneumonectomy. Four shock-plus-pneumonectomy pigs died acutely from right heart failure. When the five remaining shock-plus-pneumonectomy pigs were compared to the two control groups, pulmonary vascular resistance (PVR) increased to significantly higher levels than would be expected from the increase in PVR noted with resuscitation from shock alone and pneumonectomy alone. Right ventricular compensation maintained cardiac index in the hemorrhage-alone group and the pneumonectomy-alone group but could not maintain cardiac index in the shock-plus-pneumonectomy group, despite maximal increases in right ventricular systolic pressure, heart rate, and right ventricular end diastolic volume. These data indicated that resuscitation from shock plus pneumonectomy cannot be effectively accomplished because increased PVR leads to right ventricular failure, which limits left ventricular preload to levels that are insufficient to maintain cardiac index.

MORTALITY RATE APPROACHES 100% when pulmonary injury necessitates pneumonectomy in patients in hemorrhagic shock.¹⁻⁴ Some pathophysiologic synergy must be operative because elective therapeutic pneumonectomy is well tolerated, as is resuscitation from hemorrhagic shock when pneumonectomy is not performed. Bowling et al.¹ reported that patients in hemorrhagic shock who required pneumonectomy appeared to die of right ventricular failure, but consensus on this point is lacking.² Furthermore no experimental studies define the mechanism of this uncommon but usually fatal clinical problem. We developed a

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model of porcine hemorrhagic shock and pneumonectomy to evaluate the cardiopulmonary hemodynamic responses to resuscitation. Our data support the concept that right ventricular failure is primarily responsible for the high mortality rate in patients.

Materials and Methods

Nineteen pigs* that weighed an average of 9 kg were anesthetized with ketamine (20 mg/kg), xylazine (2 mg/kg), and atropine (0.25 mg). Animals were ventilated, after tracheostomy, to maintain arterial CO₂ between 35 and 40 mmHg. After muscle relaxation with pancuronium (0.1 mg/kg), general anesthesia was maintained with nitrous oxide (30%), oxygen (70%), and halothane (0.5%). A median sternotomy and pericardiotomy were then performed to allow placement of a transit time ultrasonic blood flowmeter around the ascending aorta to continuously measure cardiac output (CO) and Millar® catheter tip pressure transducers in the right and left ventricles, the pulmonary artery, and the right femoral artery for continuous pressure monitoring. The left femoral artery and vein were cannulated for blood withdrawal and intravenous administration of blood and resuscitative fluids. The pigs were placed on a warming blanket and under heat lamps to maintain rectal temperature at 37 C. An umbilical tape was passed around the left pulmonary hilum to be used later for left pulmonary hilar ligation.

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* Animals were handled according to National Institutes of Health Guidelines for Humane Care and Treatment.

Blood was drawn at baseline, at the end of the hemorrhage, and hourly for 4 hours after initiating resuscitation to analyze arterial blood gas and measure serum lactate and serum pyruvate.

We studied three groups of animals. All underwent a 1-hour stabilization period after induction of anesthesia. The shock-alone group (group 1, $n = 5$) had blood withdrawn from the femoral arterial line to reduce mean arterial pressure (MAP) to 50% of the baseline value within 5 minutes. Additional blood was gradually withdrawn to maintain the MAP at that level until return of shed blood would have been required to maintain such pressure. The volume of blood withdrawn was quickly determined and resuscitation performed by reinfusion of the shed blood and a volume of Ringer's lactate three times the shed blood volume. The infusion rate was adjusted to maintain left ventricular end diastolic pressure (LVEDP) at baseline for 4 hours.

The ligature around the pulmonary hilum was securely tied to approximate pneumonectomy in the pneumonectomy-alone group (group 2, $n = 5$). Ringer's lactate was infused to maintain MAP, CO, and LVEDP at baseline values for 4 hours. Nine group 3 animals were subjected to both shock and pneumonectomy. After hemorrhage the pulmonary hilum was ligated and resuscitation proceeded as in group 1. Four animals died shortly after ligation; data on the five remaining animals were used for statistical comparison to the two control groups.

Statistical analysis of these data included calculation of the mean, standard deviation (SD), and standard error of the mean (SEM) for each variable in each group at baseline, the end of the hemorrhage period, and hourly for 4 hours after initiation of resuscitation. To normalize the responses for variability in baseline values between groups and between individual animals, the difference scores between baseline and the individual time points were also calculated. The mean, SD, and SEM were calculated for these difference scores (change from baseline) in each group. All means were evaluated by analysis of variance with repeated measures in each group followed by Dunnett's test (absolute values) or Student's *t* tests (difference scores) to determine significant changes within each group across time. Between-group comparisons were evaluated by one-way analysis of variance followed by Tukey's honestly significant difference tests. Significance was determined at $p < 0.05$.

Results

There were no important differences between the mean values at baseline in the three animal groups. The four animals in group 3 who died promptly after hilar ligation demonstrated immediate severe right ventricular dilation with little filling of the left atrium and left ventricle. When right ventricular dilation reached its maximum, brady-

cardia ensued and was followed by ventricular fibrillation and death from acute right heart failure. The five survivors in this group also had acute right heart dilation, which reached its peak a few minutes after hilar ligation and then decreased without progression to bradycardia or ventricular fibrillation.

Physiologic responses to resuscitation were compared in the five survivors of group 3 to groups 1 and 2. Mean arterial pressure (Fig. 1) returned to baseline values by 1 hour after initiation of resuscitation in all three groups and remained at baseline levels through the 4-hour resuscitation period in the two control groups. However, in the shock-plus-pneumonectomy group, MAP decreased significantly below baseline by the third hour and reached levels similar to those observed during hemorrhagic shock by the fourth hour.

Cardiac index (CI, mL/min/kg) followed a similar pattern to MAP by reaching and maintaining baseline levels in groups 1 and 2. Group 3 animals exhibited a stable CI for 2 hours after resuscitation, then CI decreased significantly to levels that were approximately 50% of baseline. Heart rate was elevated in all three groups.

Stroke volume index (Fig. 2) approximated baseline values 1 hour after initiation of resuscitation in all three groups. Stroke volume index then decreased in both the shock-alone and pneumonectomy-alone groups, primarily because of an increase in heart rate. Stroke volume index decreased markedly in the shock-plus-pneumonectomy

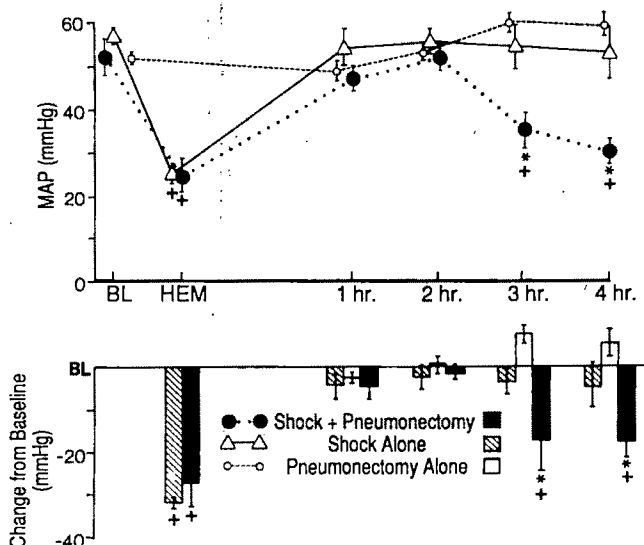


FIG. 1. Mean arterial pressure responses to shock alone, pneumonectomy alone, and shock plus pneumonectomy and resuscitation. Data are presented as the raw value in mmHg in the top panel (mean $\pm$ SEM) and as the difference scores (change from baseline in mmHg, mean $\pm$ SEM) in the bottom panel. * $p < 0.05$ for shock-plus-pneumonectomy group versus both control groups by one-way analysis of variance (ANOVA) and Tukey's HSD test. + = $p < 0.05$ from baseline by repeated measures ANOVA and Dunnett's test.

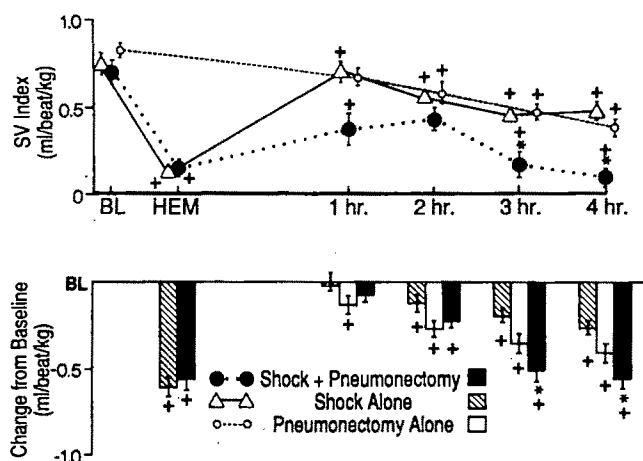


FIG. 2. Stroke volume index responses to shock alone, pneumonectomy alone, and shock plus pneumonectomy and resuscitation. Data are presented as the raw value in mL/beat/kg in the top panel (mean $\pm$ SEM) and as the difference scores (change from baseline in mL/beat/kg, mean $\pm$ SEM) in the bottom panel. * $p < 0.05$ for shock-plus-pneumonectomy group *versus* both control groups by one-way ANOVA and Tukey's HSD test. † $p < 0.05$ from baseline by repeated measures ANOVA and Dunnett's test.

group as a result of an increase in heart rate and a significant decrease in CI.

Mean pulmonary artery pressure (Fig. 3) increased significantly in all three groups by the 1-hour mark but was

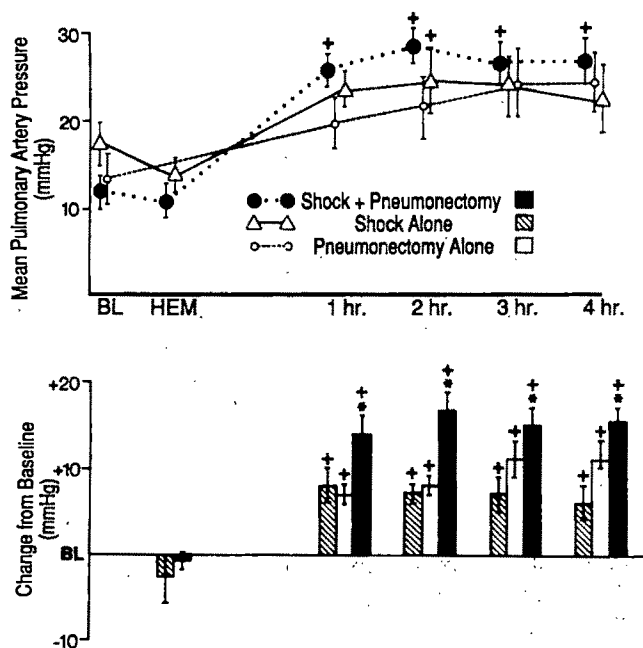


FIG. 3. Mean pulmonary arterial pressure responses to shock alone, pneumonectomy alone, and shock plus pneumonectomy and resuscitation. Data are presented as the raw value in mmHg in the top panel (mean $\pm$ SEM) and as the difference scores (change from baseline in mmHg) in the bottom panel. * $p < 0.05$ shock-plus-pneumonectomy group *versus* both control groups by one-way analysis ANOVA and Tukey's HSD test. † $p < 0.05$ from baseline by repeated measures ANOVA and Dunnett's test.

significantly higher in group 3 than in either control group when the difference scores are analyzed. Pulmonary vascular resistance index (Fig. 4) returned toward baseline levels by 1 hour after resuscitation in all three groups and remained at this level in the two control groups. In contrast pulmonary vascular resistance steadily increased in group 3.

Right ventricular systolic pressure increased significantly by hour 1 in all the groups, but when the difference scores were evaluated, it showed a significantly greater increase in group 3 than in either control group. Right ventricular diastolic pressures did not change significantly from baseline values in any group during the experiment. Left ventricular systolic pressure returned to baseline levels by 1 hour after initiation of resuscitation in all three groups. However, in group 3, left ventricular systolic pressure decreased significantly at 3 hours and decreased further by 4 hours, paralleling changes in MAP and CI.

Serum lactate and lactate-to-pyruvate ratio increased and arterial pH decreased to a similar degree by the end of the hemorrhage period in both hemorrhage groups. In the shock-alone group, lactate, lactate-to-pyruvate ratio, and arterial pH returned toward baseline at 4 hours and were not significantly different from baseline values at the end of the experiment. In contrast these lactate values

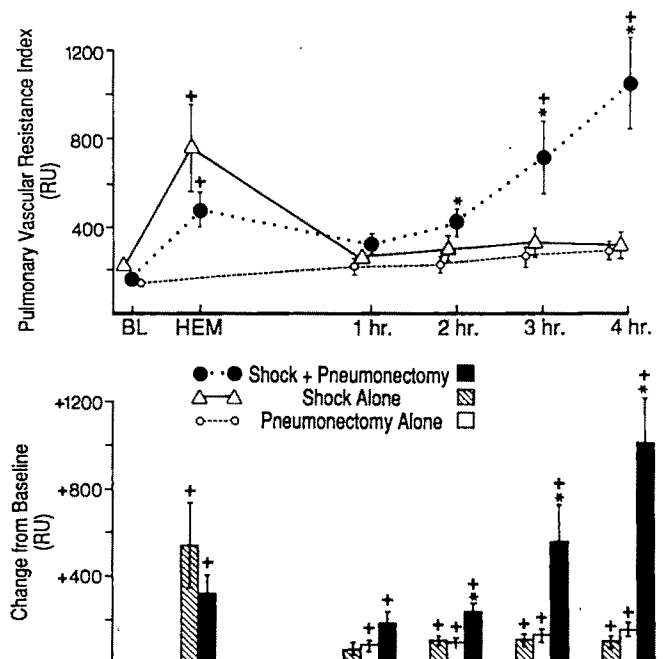


FIG. 4. Pulmonary vascular resistance index responses to shock alone, pneumonectomy, and shock plus pneumonectomy and resuscitation. Data are presented as the raw value in resistance units (RU) in the top panel (mean $\pm$ SEM) and as the difference scores (change from baseline in RU, mean $\pm$ SEM) in the bottom panel. * $p < 0.05$ shock-plus-pneumonectomy *versus* both control groups by one-way ANOVA and Tukey's HSD test. † $p < 0.05$ from baseline by repeated measures ANOVA and Dunnett's test.

never decreased toward normal in group 3 and arterial pH remained near shock levels throughout the resuscitation period. Lactate, lactate-to-pyruvate ratio, and arterial pH did not change significantly from baseline in the pneumonectomy-alone group at any point during the experiment.

Discussion

This animal model simulated the clinical problem of patients requiring pneumonectomy for central penetrating trauma or severe blunt injury associated with major blood loss. Major mortality rates are reported for such clinical conditions but the physiologic mechanism responsible for death has not been defined. In our model the shock-plus-pneumonectomy group could not be resuscitated adequately from shock. The failure of resuscitation is amply documented by deterioration in hemodynamic parameters after hour 2 of resuscitation and by the failure of arterial pH and lactate values to ever return to normal levels. Events that preceded the decline in CI and MAP in the group 3 animals included a significantly higher mean pulmonary artery pressure (MPAP) at 1 and 2 hours, a significantly higher pulmonary vascular resistance at 2 hours (mostly due to increased pulmonary artery pressure), and a significantly higher right ventricular systolic pressure without a significant increase in right ventricular diastolic pressure.

The modest increase in MPAP that we observed during resuscitation from shock alone is consistent with previous reports by Nerlich et al.⁵ and from pneumonectomy alone as reported by Crouch et al.⁶ The magnitude of the increase in MPAP in group 3 is similar to the sum of the increases caused by shock and pneumonectomy alone, and appears to be an additive effect that would result in an increased pulmonary vascular resistance.

Resuscitation from shock alone increased pulmonary vascular resistance index to levels similar to findings in several other reports.^{5,7-9} Increased thromboxane levels in pulmonary lymph⁸ and pulmonary leukostasis after resuscitation from shock¹⁰ both may contribute to pulmonary microvascular occlusion and flow alterations.

Pneumonectomy alone resulted in progressively increased pulmonary vascular resistance, which was almost entirely due to an increase in MPAP and correlated closely with previous data⁶ showing a 70% increase in pulmonary vascular resistance without a significant change in CI after acute pneumonectomy in the dog. The mechanism of increased pulmonary vascular resistance after pneumonectomy is thought to be the result of the balance between removing one of two parallel pulmonary circulation circuits, increased pulmonary vascular compliance secondary to recruitment of vessels in the remaining lung, and a decrease in compliance of the remaining larger pulmonary vessels due to increased impedance.⁶

Resuscitation from shock plus pneumonectomy increased pulmonary vascular resistance to staggering levels: 110% at 1 hour, 147% at 2 hours, and 500% by 4 hours. These changes were significantly greater than would be expected by the simple additive effects of shock and pneumonectomy alone. Factors associated with the increase in pulmonary vascular resistance in hemorrhagic shock, such as thromboxane release and pulmonary leukostasis, may interfere with the compensatory response to pneumonectomy by preventing recruitment of vessels in the remaining lung through vasoconstriction, microvascular plugging, or both.

The right ventricle has limited capacity to overcome increased resistance by developing higher interventricular pressure and, therefore, increasing right ventricular work.^{6,11,12} Right ventricular systolic pressure increased markedly in group 3 immediately after initiating resuscitation and remained at this high level for 4 hours. Because right ventricular systolic pressure did not rise further as pulmonary vascular resistance progressively increased, these data suggest that the right ventricle was generating the maximal pressure possible. This hypothesis is further supported by observations of massive right ventricular dilation during resuscitation. In addition stroke volume index was significantly less than baseline by 1 hour after initiation of resuscitation and was markedly decreased at 3 and 4 hours. Because right ventricular systolic pressure was maximal and right ventricular end diastolic volume was markedly increased (as evidenced by right ventricular dilation), the decrease in stroke volume must represent a decrease in ejection fraction and, therefore, a decrease in right ventricular function.

Possible mechanisms for this decreased right ventricular function include decreased right ventricular compliance, decreased right ventricular contractility, a progressive increase in right ventricular afterload, or a combination of these factors. Because right ventricular diastolic pressure did not increase with the marked right ventricular dilation, a decrease in right ventricular compliance was unlikely. Right ventricular myocardial inotropy should be increased as a result of enhanced sympathetic activation.¹³ Therefore the most likely explanation for decreased right ventricular function was a progressively increasing right ventricular afterload secondary to some combination of increased pulmonary vascular constriction, pulmonary microvascular plugging, and decreased pulmonary vascular compliance. The resultant right ventricular failure would have a predictable effect on MAP and CI by markedly decreasing left ventricular preload,¹⁴ which we observed in our study.

We interpret from these data that both resuscitation from hemorrhagic shock and pneumonectomy alone cause an increase in pulmonary vascular resistance that can be overcome by right ventricular compensatory mechanisms to maintain CI when either procedure occurs

alone. However, when hemorrhagic shock and pneumonectomy occur together, the increased pulmonary vascular resistance increases right ventricular afterload to a degree that exceeds right ventricular compensatory mechanisms. The result is increased right ventricular systolic pressure and right ventricular dilation with increased right ventricular volume but a markedly reduced ejection fraction and right ventricular stroke volume causing a diminished left ventricular preload. The combination of reduced left ventricular preload and decreased ventricular compliance produce a reduced left ventricular end diastolic volume at the same pressure and reduced left ventricular stroke volume. Eventually this results in decreased CI and prevents adequate resuscitation from hemorrhagic shock, leading to death. Our data suggest that resolution of this problem will require decreasing right ventricular afterload or pulmonary vascular resistance by some combination of selective pulmonary vascular dilation, prevention of pulmonary vascular plugging, or temporary mechanical support.

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Expression and Secretion of IL-2 Receptor in Trauma Patients

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The high-affinity cell-surface receptor for interleukin-2 (IL-2R) consists of the 75-kilodalton (kd) chain and a 55-kd glycoprotein known as Tac. This report examines the cellular expression of IL-2R and secretion of the soluble form of Tac in immunosuppressed blunt trauma ($n = 20$, injury severity score > 20) and thermally injured ($n = 20$, Total body surface area $> 35\%$) patients. The percentage of IL-2R-expressing peripheral blood mononuclear cells (PBMC) in mitogen-stimulated cultures from patients and age-matched normal donors was determined by direct immunofluorescence with a monoclonal anti-Tac followed by flow cytometry analysis. Levels of soluble Tac in patient sera were measured by a monoclonal antibody-based enzyme-linked immunosorbent assay. Expression of Tac antigen by mitogen-activated PBMC cultures from blunt trauma patients was transiently reduced (by as much as 40%) in 4 of 14 patients examined. Levels of serum Tac were significantly elevated ($p < 0.05$) in 15 of 20 blunt trauma patients ranging from 750 to 3000 U/mL compared with 180 to 420 U/mL in control subjects. All burn patients studied 10 to 50 days after the injury demonstrated a significant reduction (by 50% to more than 90%) in the percentage of IL-2 receptor-bearing cells. Similarly serum levels of IL-2R increased significantly ($p < 0.001$ to 0.05) in all burn patients studied, reaching concentrations as high as 5500 U/mL. These results suggest that major trauma, whether mechanical or thermal, induces alterations in the T-lymphocyte activation process. However the degree and duration of such changes may vary based on the nature of the injury.

IMPAIRMENT OF T-LYMPHOCYTE functional activity has long been implicated in the suppression of the immune response and in the frequently associated septic complications observed after traumatic injury. In accidental and surgical trauma, the reduced capacity for lymphocyte proliferation in response to T-cell-specific mitogens and alloantigens was suggested to be associated

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with activation of a suppressor T-cell population^{1,2} and dysfunction in monocyte activity.³ In patients with thermal and mechanical injuries, inadequate production of the T-cell growth factor, interleukin-2 (IL-2) was also demonstrated.^{4,5} Because IL-2 regulates the immune response through interaction with its high-affinity receptor (IL-2R) expressed by activated lymphocytes,⁶ alterations in the capacity for IL-2R expression may lead to the impairment of T-cell-mediated immune reactions. Recently we reported that the number of peripheral blood mononuclear cells (PBMC) endowed with IL-2R after mitogen stimulation is profoundly reduced in immunosuppressed patients with major burns.⁷ In addition sera from thermally injured patients contain highly elevated concentrations of the soluble form of the receptor, the 55-kilodalton (kd) molecule commonly known as Tac.⁸

The physiologic relevance of the soluble IL-2R is still unclear. However, because soluble Tac binds IL-2,⁹ it may abolish the biologic activity of this lymphokine and indirectly interfere with IL-2-regulated responses.

Our recent studies suggest that blunt trauma patients demonstrate significant immunosuppression of IL-2-regulated responses during the postinjury period.¹⁰ This may suggest further an impairment of T-cell activation similar to that reported in the burn patient.^{5,7} In this report we examine and compare alterations in T-cell activation, as manifested by the capacity of these cells to express and secrete Tac antigen, in both blunt trauma and thermally injured patients. The effect of sera from immunosuppressed blunt trauma patients on the IL-2-induced and/or regulated proliferation of normal PBMC was also assessed.

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Materials and Methods

Patients

Patient-handling procedures were performed according to the ethical standards of the Human Studies Review Committee, University of Toronto. To ensure homogeneity of the studied population of blunt trauma patients, the following criteria for enrollment were applied: an injury severity Score (ISS) of more than 20, absence of significant central nervous system trauma, and involvement of at least one major body compartment such as chest, abdomen, or retroperitoneum. Furthermore patients who received blood products were not studied within 5 days of transfusion. Conventional resuscitation and therapy were used, including surgical intervention, invasive monitoring, and use of antibiotics when indicated.

Twenty blunt trauma patients (6 female and 14 male; 17 to 64 years of age) were studied. Most patients were studied at weekly intervals following injury. Individual episodes of sepsis were examined retrospectively for each patient. Episodes were classified as 'major' if deep-seated infection was demonstrated (*i.e.*, pneumonia, intra-abdominal abscess), or if positive blood cultures were obtained. 'Minor' sepsis included simple infections (*i.e.*, urinary tract, wound) with negative blood cultures and the absence of significant systemic manifestations.

Twenty burn patients (5 female and 15 male) ranging in age from 17 to 51 years had burn injuries representing 37% to 68% total body surface area (TBSA). Nine of these patients were studied before and 11 were studied simultaneously with blunt trauma patients. Blood and serum samples were collected within 48 hours after injury and subsequently at 10-day intervals. At the time of admission, patients were resuscitated using a modified Parkland formula.¹¹ Enteral feedings were initiated within 72 hours of admission. Burn wounds were treated by twice-daily tubbings and by the topical application of silver sulfadiazine ointment (Flamazine; Smith and Nephew, Toronto, Canada). Prophylactic antibiotics were not administered.

Controls

Twelve healthy donors aged 23 to 50 years (5 women, 7 men) and 10 donors (2 women, 8 men; 24 to 45 years old) were studied with burn and blunt trauma patients, respectively.

Preparation of Peripheral Blood Mononuclear Cell Cultures

Peripheral blood mononuclear cell cultures from the studied patients and controls were prepared by gradient centrifugation on Ficoll-Hypaque, as previously described.¹² Cells collected from the interface were washed thoroughly and resuspended at a final concentration of 1

$\times 10^6$ cells/mL in a complete tissue culture medium (TCM) consisting of RPMI 1640 supplemented with a pretested batch of fetal calf serum (10% v/v), antibiotics, and 5×10^{-5} M 2-mercaptoethanol.

Activation of PBMC Cultures and Enumeration of Tac(+) Cells

Peripheral blood mononuclear cell cultures were cultivated with concanavalin A (Con A, $10 \mu\text{g/mL}$) for 72 hours in TCM. Cells were then washed, stained with a monoclonal anti-IL-2R phycoerythrin- or fluorescein-conjugated antibody (Becton Dickinson, Lincoln Park, NJ) and analyzed on an EPICS V Flow Cytometer (Coulter Electronics, Hialeah, FL). The percentage of Tac(+) (IL-2R-expressing) cells was determined by enumeration of the stained cells accounting for nonspecific fluorescence and background staining by using appropriate controls, including normal mouse IgG1 and staining of unstimulated PBMCs.

Determination of Serum Tac (IL-2R) Levels

Soluble Tac concentrations in posttrauma and postburn serum samples were determined by an enzyme-linked immunosorbent assay based on monoclonal antibodies to two different epitopes of the 55-kD Tac molecule (T Cell Sciences Inc., Cambridge, MA). The assay was performed according to the manufacturer's specifications. Each sample was tested twice within 24 hours after thawing.

Effect of Post-trauma Serum on Proliferative Response of Normal Human PBMC

The immunoregulatory potential of sera from blunt trauma patients was examined in the mixed lymphocyte reaction (MLR) and IL-2-induced proliferation of normal PBMC as described before.¹² Briefly, PBMC at a concentration of 5×10^5 cells/mL were cocultured with mitomycin C-treated human lymphoblastoid cells (2.5×10^5 cells/mL).¹³ Exogenous IL-2 (Electro-nucleonics, Silver Spring, MA) was used at concentrations ranging from 5% to 20% (v/v).

The incorporation of tritiated thymidine [^3H]TdR in the MLR and IL-2-activated cultures was measured on day 6 after a 16-hour pulse. Patients and control sera were added to the studied cultures at initiation at a concentration of 10% (v/v).

Statistics

The statistical significance was estimated by Student's *t* test and a *p* value less than 0.05 was considered significant.

Results

Patients

All blunt trauma patients presented in this study survived. However septic complications developed in 11 of the 20 patients studied (Table 1). Of note 8 of these 11 infections occurred in patients with an ISS ≥ 30 . Only 3 of the 11 occurred in the less severely injured group (ISS < 30). The hospitalization period ranged from 10 to more than 90 days and the number of studies performed in each patient varied from 2 to 7. Six of twenty burn patients developed overwhelming sepsis and died between 16 to 35 days after burn. The mean hospitalization period for the surviving patients was 60.8 days. Burn patients were tested two to six times during the postburn period, depending on their outcome.

Assessment of Patients' Immune Status

Alterations in the immune status of the studied blunt trauma and burn patients were described in detail in four independent studies.^{7,8,10,12} Both blunt trauma and burn patients demonstrated a significant suppression of the humoral immune response in pokeweed mitogen-activated PBMC cultures.^{10,12} The immunosuppression of T-cell alloreactivity and the reduced secretion of IL-2 were observed in burn patients^{7,12} and coincided with a decreased percentage of IL-2R-expressing cells.^{7,14}

Expression of IL-2R (Tac Antigen) During the Post-trauma Period

The percentage of IL-2R-bearing cells in Con A-activated PBMC cultures from blunt trauma patients was de-

Alterations in the Capacity for Expression of IL 2R (Tac) by Mitogen-activated PBMC Cultures from Blunt Trauma and Burn Patients

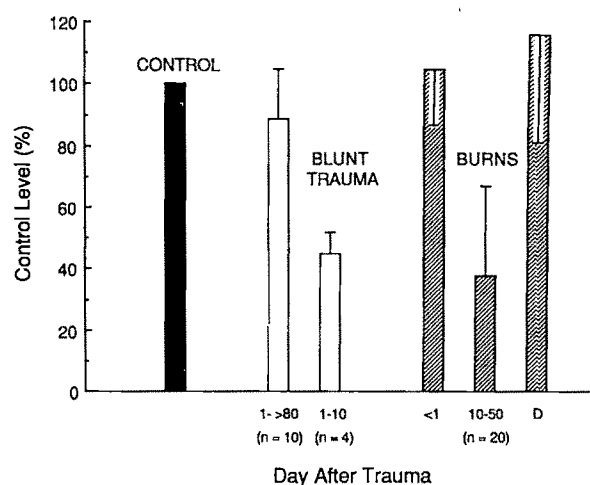


FIG. 1. Alterations in the capacity for expression of IL-2R (Tac) by mitogen-activated peripheral blood mononuclear cells from blunt trauma (□) and burn (▨) patients. The mean levels of Tac-positive cells determined in individual patients throughout the postinjury period are expressed as a percentage of control (■).

termined by measuring the green fluorescence of 10^4 cells stained with anti-Tac antibody on a flow cytometer. Figure 1 represents alterations in the capacity for expression of IL-2R (Tac antigen) by Con A-activated PBMC cultures from both blunt trauma and burn patients. The mean levels of Tac-positive cells were determined in individual patients throughout the postinjury period and were then expressed as a percentage of control (Fig. 1). Ten of fourteen patients who were studied at least twice demonstrated no significant alterations in the percentage of IL-2R-expressing cells compared with normal donors (Fig. 1). In the remaining 4 patients (numbers 3, 5, 6, and 9), a transient but significant ($p < 0.05$) reduction in the percentage of activated T cells was apparent in tests conducted within 10 days of the injury (Fig. 1). At that time the number of Tac-positive cells in these patients was reduced by more than 50% compared to both the patient's baseline (discharge time) and control levels. The percentage of IL-2R-expressing cells returned to control level during the second week of hospitalization.

The effect of burn injury on cell-surface Tac was apparent in all patients studied (Fig. 1). In accordance with our previous results,^{7,14} a significant ($p < 0.001$ to 0.05) reduction in the number of these cells was observed in immunosuppressed burn patients monitored between 10 to 50 days after injury (Fig. 1). The mean level of activated (Tac-expressing) T cells in this patient population was reduced by more than 60% compared with control. Our earlier studies demonstrated that the percentage of IL-2R-bearing cells is particularly effected in nonsurviving burn patients.⁷ At the time of the survivors' discharge

TABLE 1. Blunt Trauma Patients' Data

Patient	Age	Sex	ISS	Injury	Infection
1	54	F	21	MVA	No
2	23	M	27	MVA	No
3	67	M	19	Pedestrian MVA	Major
4	25	M	43	Pedestrian MVA	Minor
5	42	F	22	MVA	No
6	40	M	21	MVA	Major
7	20	F	27	MVA	No
8	17	F	29	MVA	No
9	58	F	45	MVA	Major
10	33	M	41	MVA	Major
11	21	M	29	MVA	No
12	41	M	38	Industrial injury	Major
13	36	M	38	Industrial injury	Minor
14	64	M	17	Pedestrian MVA	No
15	43	M	50	Pedestrian MVA	Major
16	23	M	50	Industrial injury	Minor
17	37	M	30	MVA	Major
18	21	M	22	MVA	No
19	38	M	29	Industrial injury	Major
20	23	F	21	Pedestrian MVA	No

Control: F/M, 2/10; age, 24 to 45.

ISS, injury severity score; MVA, Motor vehicle accident; F, female; M, male.

(Fig. 1D), the percentage of IL-2R-expressing cells returned to normal or higher levels not different from those observed at admission (Fig. 1, > 1).

Secretion of Serum IL-2R During the Post-trauma Period

The levels of serum Tac in blunt trauma patients were determined at various time points following injury, at 1 to 2 weeks apart. Of 20 patients presented in this study, 11 demonstrated significantly elevated ($p < 0.05$) concentrations of serum IL-2R, ranging from 580 to 3000 U/mL throughout the study period (Fig. 2). In four patients (numbers 5, 7, 8, and 18), elevations in the serum IL-2R level were observed only sporadically (range, 650 to 1100 U/ml) (Fig. 2). The remaining patients ($n = 5$) demonstrated normal concentrations of serum-borne IL-2R (Fig. 2).

Thermal injury-induced changes in the level of serum IL-2R can be observed within 24 hours after the injury.⁸ In most (16 of 20) burn patients presented in this study, a significant ($p < 0.05$) rise in soluble Tac level was apparent at the time of admission, with a mean of 1056 ± 637 U/mL compared with 367 ± 92 U/mL in control (Fig. 2, < 1). The levels of serum Tac increased further (mean, 2530 ± 1336 ; range, 700 to 5510 U/mL) in burn patients tested 10 to 50 days after burn (Fig. 2). These results confirm our previous observations of highly significantly ($p < 0.001$) elevated serum IL-2R concentrations in immunosuppressed burn patients.^{8,14} In the sur-

vivors the levels of serum IL-2R declined to a mean of 1187 ± 211 U/mL at discharge (Fig. 2D), remaining significantly higher ($p < 0.001$ to 0.05) than normal control and comparable to those in most blunt trauma patients.

Effect of Post-trauma Serum on the IL-2-induced Proliferation and MLR of Normal PBMC

The proliferative response of freshly isolated human PBMC observed in the presence of exogenous IL-2 is thought to be the result of up-regulation of IL-2R levels similar to that demonstrated by activated lymphocytes.¹⁵ Our previous studies demonstrated that postburn sera have a strong capacity to inhibit proliferative responses of normal lymphocytes to both alloantigen and exogenous recombinant IL-2.¹⁶ In the present study, the effect of serum from 10 blunt trauma patients was assessed in a similar system. Patient selection was based solely on the availability of sufficient quantities of serum for both studies. Sera from 5 of 10 patients studied demonstrated a moderate to significant ($p < 0.05$) inhibitory effect on IL-2-triggered proliferation of normal PBMC. The DNA synthesis in such cultures as measured by [³H]TdR incorporation was reduced by 25% to more than 50% compared with the control response determined in the presence of normal human and autologous serum (Table 2). However alloproliferation in MLR was not affected in the presence of the same or other (not shown) blunt trauma serum samples tested simultaneously (Table 2). Further-

Alterations in the Capacity for Secretion of IL 2R in Blunt Trauma Patients

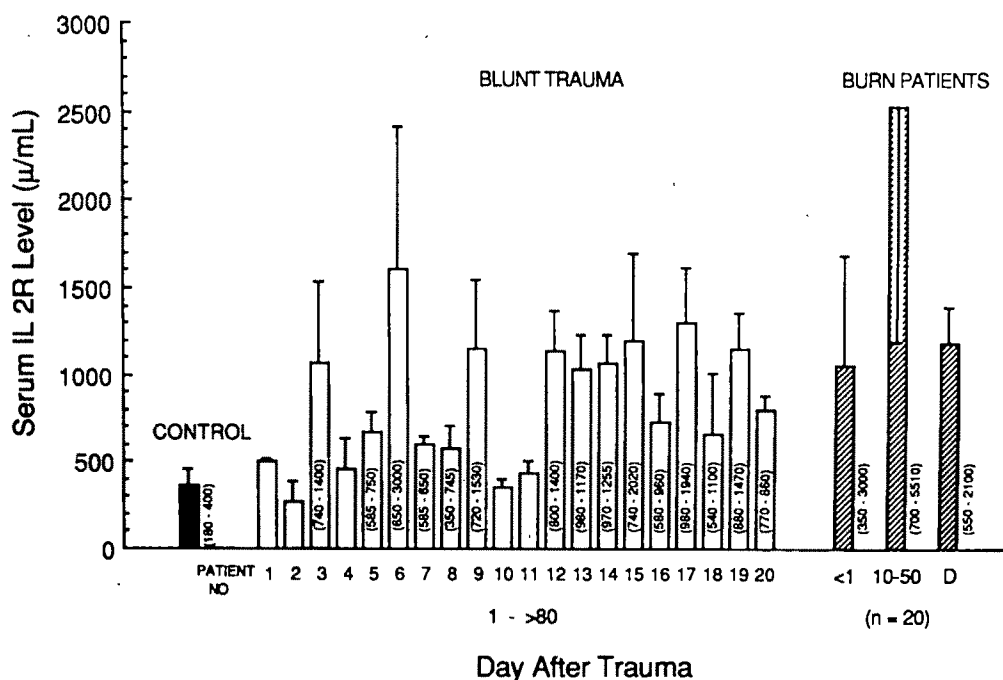


FIG. 2. Serum IL-2R (Tac) levels in blunt trauma and burn patients during the postinjury period. The levels of soluble Tac in serum samples from individual blunt trauma patients (□) and the mean concentrations of serum Tac in burn patients (■) are depicted.

TABLE 2. Effect of Post-trauma Serum on IL-2-mediated Proliferation of Normal PBMC*

Patient (Test #)	Serum IL-2R U/mL	³ H]TdR Incorporation (CPM)†	
		IL 2 (20% v/v)	MLR
4 (2)	680	8017 ± 1500	82,500 ± 8200
6 (1)	650	8500 ± 370	53,300 ± 13,700
(2)	2850	8400 ± 500	72,800 ± 8500
(3)	1800	8600 ± 800	82,900 ± 6100
7 (3)	650	8000 ± 880	63,300 ± 8900
9 (1)	1530	5900 ± 750	73,500 ± 2900
(2)	1180	5300 ± 400	66,200 ± 500
16 (1)	980	6400 ± 2100	60,300 ± 11,200
(2)	1940	15,700 ± 1400	48,700 ± 3200
Control (n = 5)	313 ± 90	11,650 ± 2345	63,300 ± 3500

PBMC, peripheral blood mononuclear cell.

* Normal PBMC cultures were supplemented with blunt trauma patients' (Patient) or normal human (Control) serum at a concentration of 10% (v/v). IL-2-mediated cell proliferation generated in the presence

of exogenous or endogenous (MLR) lymphokine was then measured on day 6 as described in Materials and Methods.

† Mean ± SEM.

more no correlations between the suppressive activity of a serum and its soluble IL-2R content were observed (Table 2).

Discussion

Abnormalities of T-cell function have been suggested as a principal cause of the reduced host resistance in trauma patients.^{16,17} However molecular mechanisms of injury-induced (or related) alterations in the biological response of T lymphocytes to an activating signal (*i.e.*, antigen or mitogen) have been studied only recently. Due to the heterogeneity of the trauma patient population, such studies have been restricted almost entirely to patients with major burns.^{5,7,14,18} Recent studies by Faist et al.⁴ demonstrated the impairment of CD4+ cell function manifested by the inhibited production of IL-2 and associated reduction in expression of IL-2R in polytraumatized patients. However those studies included blunt trauma, penetrating trauma, central nervous system-injured, and postoperative surgical patients. The present study examined a well-defined group of blunt trauma patients who were followed sequentially during their hospitalization period in the same center.

We demonstrated previously that helper T-cell-dependent polyclonal immunoglobulin secretion is significantly reduced in this patient population.¹⁰ Furthermore suppressed antibody production was paralleled by a decrease in the proliferative response to T-cell-dependent pokeweed mitogen (PWM).¹⁰ Normally mitogen-induced proliferation of peripheral blood T cells is initiated and regulated by IL-2 through triggering of IL-2R-expressing lymphocytes.⁶ Thus a reduction in IL-2 production and/or an inability of T cells to respond to IL-2 may result in suppression of their proliferation. However we have not observed significant alterations in the production of IL-2 in blunt trauma patients.¹⁹ Furthermore the present study

demonstrates that expression of the cell-surface IL-2R is not significantly affected in most of these patients (Fig. 1). Although the possibility of significant intra- and interpatient fluctuations cannot be dismissed and should be further examined in frequently sampled donors, the above results suggest that T-lymphocyte activation is not inhibited in blunt trauma. This assumption may be further supported by the essentially normal lymphoproliferative response of blunt trauma patients to alloantigens.¹⁰

In contrast to blunt trauma patients, the capacity for expression of Tac antigen is profoundly affected in PBMC cultures from burn patients (Fig. 1). Thus the present study and our previous reports^{7,14} confirm that in the burn patient, the reduced proliferative response to mitogens and the definite patterns of altered T-cell reactivity are associated with the impaired expression of functional, high-affinity IL-2 receptors.

The high-affinity IL-2R is a heterodimeric membrane complex composed of two IL-2-binding moieties: the 55-kd (Tac, IL-2R) glycoprotein and a second 70- to 75-kd (IL-2R) chain distinct from Tac.²⁰ The Tac molecule participates in the formation of both high- (biologically active) and low-affinity IL-2R.²¹ The function of the latter form of Tac is still unclear but it has been suggested to play a negative regulatory role in T-cell growth and clonal expansion.²¹ Similarly the physiologic role of the soluble Tac is presently unknown. Elevated levels of soluble IL-2R are characteristically found in patients with undifferentiated lymphoblastic lymphomas, human immunodeficiency virus infections, and active sarcoidosis.²²⁻²⁵ We have recently reported that in the burn patient, concentrations of serum IL-2R are elevated up to 50 times above normal levels.⁸ As demonstrated in the present and earlier studies, an increase in the serum Tac content is apparent within hours of the injury and is further augmented during the postburn period of immunosuppression (Fig. 2). In

comparison with thermally injured patients, serum concentrations of IL-2R in blunt trauma subjects were moderately increased throughout the study period (Fig. 2). It should be noted, however, that the levels of serum Tac in the majority of blunt trauma patients, although considerably lower than those in immunosuppressed burn patients, were significantly elevated above normal levels (Fig. 2).

Secreted IL-2R is derived from viable cells and requires *de novo* protein synthesis.²⁵ Both the membrane-bound and the soluble form of Tac are products of the same gene.²⁶ Thus high concentrations of serum Tac are usually observed in clinical conditions characterized by the presence of many CD 25+ (IL-2R-expressing) circulating PBMC.²⁷ The cellular origin of soluble Tac in both blunt trauma and burn patients is not clear, but it has been suggested to derive primarily from CD4+ and CD8+ T cells.⁸ The mechanisms regulating IL-2R secretion by these cells are also unknown. Our recent studies in the burn patient suggest that, similar to its cell-surface counterpart,¹⁵ soluble Tac synthesis and/or secretion may be up-regulated by IL-2 itself (manuscript in preparation). Burn serum-associated Tac is capable of specific binding to its ligand immobilized on a solid-state matrix.²⁸ Furthermore immunosuppressive activity of postburn serum generally is correlated with soluble IL-2R content, suggesting that this molecule may represent a specific mediator of immunosuppression after burn injury.²⁹ It is not clear if sera from blunt trauma patients can also demonstrate significant immunosuppressive activity. In the present study we observed a marked reduction of exogenous IL-2 activity in a culture milieu containing serum from blunt trauma patients (Table 2). Therefore it is possible that an elevation of serum IL-2R levels may interfere with IL-2-regulated responses to some degree. However, because the production of this lymphokine in blunt trauma patients appears to be sustained within the normal range¹⁹ and these patients sera do not effect the MLR of normal PBMC (Table 2), significant contribution by serum-borne soluble mediators toward immunosuppression in this patient population is questionable.

However elevated concentrations of IL-2R in post-blunt-trauma serum may be associated with sepsis. In the present study, 11 patients developed significant septic complications. Of these 11, 9 patients had persistently elevated concentrations of IL-2R. The two remaining patients had essentially normal IL-2R levels throughout, although one patient could only be sampled late after his injury (40 days) and the other patient was well until just before discharge when he developed pneumonia. Of the four patients with only sporadic increases, none developed septic sequelae. The five patients with persistently normal IL-2R levels contained the two septic patients mentioned above.

From these results it is clear that there is some association between persistent elevations in serum IL-2-receptor level and risk of septic complications. Although more frequent sampling would be desirable, it appears that increased receptor levels do not necessarily reflect individual septic episodes because sporadic elevations were not associated with infections, and 9 of 11 patients with sepsis had persistent elevations throughout their hospital course, both before infection and after complete recovery. Rather it appears that persistently elevated IL-2R levels may signal an increased risk for development of sepsis and may therefore be helpful, in a prognostic sense, to identify those patients in whom septic complications are more likely to occur.

The findings presented in this and earlier studies^{7,8,10,14} suggest that trauma, whether mechanical or thermal, may alter the T-cell activation pathway. However the mechanisms involved in these processes and the resulting changes in the biological activity of T-cell subsets may vary considerably based on the nature of the injury. Thus, despite the similarities in clinical manifestations of injury-related immunosuppression, its pathophysiology may be quite distinct.

Acknowledgment

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Addition of Parenteral Cefoxitin to Regimen of Oral Antibiotics for Elective Colorectal Operations

A Randomized Prospective Study

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The efficacy of cefoxitin, a perioperative parenteral antibiotic, combined with mechanical bowel preparation and oral antibiotics to prevent wound infections and other septic complications in patients undergoing elective colorectal operations, was examined in a prospective randomized study. All 197 patients who completed the study received mechanical bowel preparation and oral neomycin/erythromycin base. In addition a perioperative parenteral antibiotic was given in three divided doses to 101 patients. The other 96 patients received no parenteral antibiotics. The overall incidence of intra-abdominal septic complications was 7.3% (7 of 96) in the control group (no cefoxitin) and 5% (5 of 101) in the treatment group (cefoxitin). This difference was not statistically significant. The incidence of abdominal wound infection was 14.6% in the control group and 5% in the treatment group, a statistically significant difference ($p = 0.02$). The addition of perioperative parenteral cefoxitin greatly reduced the incidence of wound infections in patients undergoing elective colorectal operations who had been prepared with mechanical bowel cleansing and oral antimicrobial agents.

PREPARATION TECHNIQUES OF the large intestine for elective operations of the colon and rectum have evolved so that the current standard of surgical care mandates the use of mechanical cleansing combined with antimicrobial agents. Some debate exists regarding the relative importance of the preoperative administration of oral antibiotics compared with the use of parenteral antibiotics in the perioperative period.¹ Specifically the addition of parenteral antibiotics to the regimen of mechanical cleansing and the use of oral antibiotics has not consistently reduced the number of septic complications associated with elective colorectal procedures.^{2,3} As a result of these inconsistencies and in light of increased pressures for cost containment, surgeons are being asked to reassess the common clinical practice of combining oral and parenteral antibiotics as prophylaxis in this situation.

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Our aim was to determine the efficacy of the addition of a second-generation cephalosporin, cefoxitin (Mefoxin; Merck Sharp & Dohme, West Point, PA), to the regimen of mechanical cleansing and the use of oral antibiotics in a randomized prospective study. Cefoxitin is an antibiotic with activity against gram-negative aerobes and anaerobes, the most common pathogens isolated from infections associated with colorectal procedures.⁴ This feature makes it one of the most commonly used prophylactic antibiotics in colorectal procedures. Our study compares the rates of wound infection with the rates of intra-abdominal infections in two groups of patients. One group received cefoxitin in addition to mechanical preparation and oral antibiotics, and the other group did not.

Materials and Methods

The study population consisted of 197 patients who underwent elective colorectal operations at the Lahey Clinic Medical Center between January 4, 1985, and March 25, 1988. Prior approval for the study was obtained from the Institutional Review Board of the Lahey Clinic Medical Center.

All patients 18 years of age and older who were undergoing elective operations on the colon or rectum by the abdominal route were potentially eligible. Previous penicillin or cephalosporin allergy, use of oral or parenteral antibiotics within 72 hours before operation, use of probenecid within 1 week before operation, and evidence of colonic obstruction that would preclude adequate mechanical bowel preparation were criteria for exclusion. In addition patients requiring parenteral antibiotic prophylaxis for cardiac valve disease and patients having *in situ* foreign material, such as vascular grafts, prosthetic valves or joints, and cardiac pacemakers, were not eligible.

Supported by a grant from Merck Sharp & Dohme, West Point, PA. Address reprint requests to Dr. David J. Schoetz, Jr., Department of Colon and Rectal Surgery, Lahey Clinic Medical Center, 41 Mall Rd., Burlington, MA 01805.

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This study was conducted as an open-label randomized observer-blinded trial. Randomization was achieved by means of a multiplicative congruent linear method of pseudorandom number generation using a Hewlett Packard Series 41 program SSTI-04A (Rockville, MD). Blocks consisted of 10 patients randomized to cefoxitin and 10 patients to no cefoxitin. Sealed opaque envelopes were used and were prepared in the Department of Research, where they were numbered consecutively. Consent for entrance into the study was obtained in writing from the patient by physicians in the Department of Colon and Rectal Surgery and the Department of General Surgery. Four of five attending surgeons (JAC, JJM, DJS, and MCV) and all patients were not informed of the results of randomization.

All patients received a standard mechanical bowel preparation and oral antibiotics in a schedule as outlined in Table 1. The control group received no parenteral antibiotics. The treatment group received three doses of cefoxitin, 2 g each, with the first dose administered within 60 minutes before incision, the second dose in the recovery room at 6 hours, and the third dose 6 hours thereafter.

Shaving of the abdomen was performed within 60 minutes before the incision was made. The skin was prepared with povidone-iodine (Betadine; Purdue Frederick Co., Norwalk, CT) solution. Paper drapes were used in all instances. Adhesive skin barriers and wound protectors were used for patients without a pre-existing stoma. Fascial closures were accomplished with a single layer of absorbable monofilament sutures using a continuous mass closure technique. Subcutaneous sutures were not used, and the skin was closed with stainless steel clips. No attempt was made to standardize operative technique.

Wounds were inspected daily. For purposes of this study, wound infection was defined as purulent wound drainage; the exudate either spontaneously drained or was expressed after removal of skin staples over a clinically suspect area of the wound. Cultures were obtained whenever possible.

Other complications of infection were recorded and managed appropriately according to the clinical circumstance. Intra-abdominal sepsis was diagnosed in patients who had a fever after operation and for whom no other

TABLE 2. Comparison of Control and Treatment Groups

Factor	Control (No Cefoxitin) n = 96	Treatment (Cefoxitin) n = 101
Sex (male:female)	62:34	64:37
Age, median (range)	54 (18-96)	56 (22-80)
Disease*		
Carcinoma	43	48
Inflammatory bowel disease		
Chronic ulcerative colitis	20	16
Crohn's disease	11	6
Indeterminate disease	—	1
Diverticular disease	14	20
Polyp	6	8
Familial polyposis	4	2
Miscellaneous	1	2
Patients taking steroids	30	17

* Five patients had two diagnoses.

source of infection could be demonstrated on complete investigation or a documented intra-abdominal source by radiographic investigation, such as in the case of abscesses within the peritoneal cavity or anastomotic leakage.

Records were reviewed by one of the authors (PLR). Follow-up was obtained by office visits 1 and 4 months after operation. Late complications of infection were recorded.

The randomization code was broken after data had been compiled. Statistical analysis was carried out by paired two-tail t test (program BMDP-3D) and Miettinen's modification of the Fisher exact test and the Mantel-Haenszel chi test described by Rothman and Boice⁵ using a CALC41 System (Tacit Logic Systems, Inc., Tigard, OR) in a microcomputer with 80287 coprocessor. Differences at the level of two-tail $p < 0.05$ were considered statistically significant.

Results

Of the 225 randomized patients, 28 were withdrawn from the study: because of improper dose of study drug, 10 patients; because of change in operative strategy, 9 patients; because of ineligibility that was not recognized, 7 patients; and due to patient request, 2 patients. Data from the remaining 197 patients (126 men and 71 women) were analyzed. The median age was 55 years (range, 18 to 96 years). The control group (no cefoxitin) included 96 patients, and 101 patients received cefoxitin. Comparisons between the groups and the indications for operation are given in Table 2. The actual operative procedures are summarized in Table 3 for both groups. Carcinoma was the most common indication for operation in this series. Data for septic complications directly attributable to the colorectal nature of the operation are presented in Table 4.

Wound infection occurred in 14 patients in the control group (14.6%) and in 5 patients in the treatment group

TABLE 1. Bowel Preparation

Day	Preparation
1	Clear liquids Citrate of magnesia, 10 fluid oz.—Afternoon Saline enemas until clear—Evening
2	Clear liquids Citrate of magnesia, 10 fluid oz.—Morning Neomycin 1 g, erythromycin base, 1 g— Orally at 1 P.M., 2 P.M., 11 P.M.*
3	Operation at 8 A.M.

* Times amended for later operation.

TABLE 3. Operations Performed

Operation	Control (No Cefoxitin)	Treatment (Cefoxitin)	Total
Abdominoperineal resection	6	3	9
Anterior resection	4	11	15
Low anterior resection	7	15	22
Total colectomy, ileorectal anastomosis	7	5	12
Colostomy closure	2	3	5
Descending colectomy	1	—	1
Ileocolic resection	3	2	5
Left hemicolectomy	4	6	10
Ileoanal reservoir	16	12	28
Right hemicolectomy	12	12	24
Sigmoid colectomy	21	22	43
Transverse colectomy	1	—	1
Total colectomy, ileostomy	7	5	12
Loop colostomy	2	1	3
Hartmann resection	1	—	1
Total proctocolectomy	2	3	5
Small bowel and colon resection	—	1	1
Total	96	101	197

(5%). This difference is statistically significant ($p = 0.02$). Because the number of patients taking steroids at the time of operation was substantially higher in the control group, this specific issue was addressed by analyzing data with the Mantel-Haenszel chi test, controlling for steroid use as a confounding variable. Again the incidence of wound infection was significantly higher in the control group ($p = 0.045$).

Anastomotic leakage occurred in 4 of 78 (5.1%) anastomoses in the control group and in 3 of 89 (3.4%) anastomoses in the treatment group. This difference is not statistically significant ($p = 0.67$). Of the seven instances of leakage, four occurred in patients undergoing low anterior resection for either carcinoma of the rectum or villous adenoma; the other three occurrences were in patients undergoing anastomosis for Crohn's disease.

Intra-abdominal sepsis was recognized in two different forms. Pelvic cellulitis, characterized by fever, leukocytosis, lower abdominal pain, and purulent drainage from the ileal reservoir, occurred in two patients undergoing construction of an ileoanal reservoir; one patient was in the control group and the other patient was in the treatment group. Cultures from the abdominal drain revealed

Escherichia coli in one patient and *Staphylococcus aureus* and *Pseudomonas* in the other patient. Based on these cultures, specific antimicrobial therapy was administered for 7 days without the need for operative intervention. Pelvic abscesses occurred in two patients in the control group (2%) and in one patient in the treatment group (1%). Two patients required surgical intervention, and in the third patient, the abscess resolved after spontaneous drainage from a Hartmann pouch. The difference between the two groups in overall rates of the incidence of intra-abdominal sepsis is not statistically significant ($p = 0.68$).

No patient experienced substantial adverse effects from either the oral antibiotics or the cefoxitin.

The results of bacteriologic study are outlined in Table 5.

Discussion

Mechanical cleansing of the colon before elective colorectal operations has long been recognized as an essential part of preoperative preparation.⁶ Because the colon is a rich reservoir of bacteria, purgation of fecal contents substantially reduces the number of potentially pathogenic bacteria.

With the advent of antimicrobial agents, oral preparation was added to mechanical cleansing in an attempt to reduce further the incidence of septic complications. In 1953 Poth⁷ reviewed the data on available drugs and concluded that neomycin was an excellent oral agent because of its poor absorption from the gastrointestinal tract and consequent low toxicity. He noted overgrowth of yeast in the intestine with its use. Studies by Cohn and Rives⁸ demonstrated that the addition of intraluminal neomycin and tetracycline decreased the incidence of septic and anastomotic complications in an experimental model. Nichols and associates⁹ documented appreciable reduction in intraluminal bacteria by the use of oral antibiotics. In fact, as a result of this study, the authors⁹ demonstrated the need for drugs directed at both aerobes and anaerobes. Based on their results, a combination of neomycin and erythromycin base in the dosage schedule depicted in Table 1 was studied retrospectively¹⁰ and applied prospectively,¹¹ and a meaningful reduction in the number of septic complications resulted when these antibiotics were used with mechanical cleansing.

Despite the fact that the neomycin/erythromycin base

TABLE 4. Operation and Specific Septic Complications

Complication	Control (No Cefoxitin)		Treatment (Cefoxitin)	
	Total	Taking Steroids	Total	Taking Steroids
Wound infection	14	6	5	2
Anastomotic leakage	4	1	3	1
Intra-abdominal abscess/cellulitis	3	2	2	0

TABLE 5. *Bacteriology of Infected Wounds*

Complication	Number
Control (no cefoxitin): 9 of 15 wounds	
<i>E. coli</i>	3
Enterococcus	3
<i>S. aureus</i>	3
Gram-negative rods (other)	5
Alpha-hemolytic streptococcus	1
Treatment (cefoxitin): 5 of 5 wounds	
<i>E. coli</i>	3
Enterococcus	2
<i>S. aureus</i>	2
Other	1

(the Nichols-Condon prep) has become the most widely used oral antibiotic regimen, any nonabsorbable combination or single agent that is highly effective against both aerobic gram-negative rods and anaerobes has also been shown to be effective for colorectal cleansing before operation.¹²

With the development of parenteral antibiotics, attempts were made to substitute these agents for oral agents. Results of studies up to 1983, as reviewed by Guglielmo and associates,¹³ were mixed. Antimicrobial agents with a spectrum limited to either aerobes or anaerobes alone are usually ineffective in reducing septic complications of colorectal operations when administered parenterally as a substitute for oral antibiotics.

Crucial to our study was the question of the benefit of combining parenteral and oral antibiotics to confer additional protection against septic complications compared with the benefit of either regimen alone. In recent analyses of available studies, the majority conclusion has been that 'combining oral and parenteral drugs should be unnecessary in most patients.'¹³ Unfortunately most of the antibiotics administered parenterally were not active against both aerobes and anaerobes, and, consequently, the conclusions of these analyses are questionable.

Cefoxitin is a second-generation cephalosporin that is bactericidal against a wide range of potential colonic pathogens, including gram-positive cocci, gram-negative bacilli, and anaerobes.⁴ Hoffmann and associates¹⁴ reported a small series in which cefoxitin was randomly added to one half of a group of patients undergoing mechanical preparation and oral kanamycin (Kantrex; Bristol Laboratories, Syracuse, NY) therapy. They¹⁴ demonstrated appreciable reduction in rates of wound infection with the addition of parenteral cefoxitin. A potential weakness of this study¹⁴ was the deletion of an oral antianaerobic agent in the control group. Consequently the favorable results may have been the result of this omission rather than because of the addition of cefoxitin.

Our study was designed to compare numbers of septic complications in two groups of patients undergoing elective colorectal operations by means of the abdominal

route. Specifically cefoxitin was added in a randomized prospective manner to the most widely used oral antibiotic combination that has been proved highly effective. Results indicate that the addition of cefoxitin confers appreciably more protection against the development of wound infection (5% versus 14.6%; $p = 0.02$). On the other hand, anastomotic leakage and intra-abdominal sepsis were not affected by addition of cefoxitin. The former is usually the result of a technical failure and would not be expected to be altered substantially by prophylactic antibiotics; the latter might be expected to be affected, but the number of occurrences in the two groups is too small to draw statistically valid conclusions.

Our data support the addition of perioperative parenteral cefoxitin to the regimen of mechanical cleansing and the use of oral neomycin/erythromycin base to reduce the risk of abdominal wound infection in patients undergoing elective colorectal operations.

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Effects of Age and Body Composition on the Metabolic Responses to Elective Colon Resection

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Advancing age tends to be accompanied by predictable changes in organ-system function and body composition, as well as an increased prevalence of various diseases. Our knowledge of the metabolic responses to surgical stress is derived largely from studies of young and middle-aged individuals. Whether these responses are altered in the elderly is not well established; the characteristic changes in metabolic function and body composition that occur in the elderly may limit their ability to respond adequately and to survive severe or complicated surgical procedures. To evaluate the effects of age and differences in body composition on the metabolic responses to surgery, we studied 20 active and otherwise healthy men aged 43 to 77 years, before and after elective colon resection. Age was not related to weight or total body water (TBW) in the patients studied. Resting preoperative energy expenditure was strongly dependent on TBW (reflecting lean body mass) and age ($r^2 = 0.80$, $p < 0.001$), and to TBW and creatinine excretion (reflecting muscle mass) ($r^2 = 0.85$, $p < 0.001$). Energy expenditure increased $18 \pm 2\%$ (range, 4% to 40%) after operation but this response was unrelated to age. Postoperative urine nitrogen was related to body weight or TBW, but not to age. Serum glucose, cortisol, white blood cell count, and C-reactive protein responses were also independent of patient age. The metabolic responses of generally healthy men to a moderate surgical stress do not vary with age in the range studied. The metabolic responses to more severe or prolonged stress may be altered with advancing age and changes in body composition, and in patients with concomitant diseases.

ADVANCING AGE DURING adulthood is recognized as a marker both for physiologic changes in almost every organ system and an increased prevalence of specific disease processes.^{1,2} Advancing age also tends to be accompanied by predictable alterations in body composition and in metabolic and endocrine function. Our knowledge of how these changes may alter the met-

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abolic responses of the elderly to surgical stress is limited, despite an increasing understanding of these responses in generally healthy young and middle-aged individuals.³

The changes in intermediary metabolism that occur after surgery and trauma support host defence, wound repair, and a variety of proliferative, synthetic, and transport processes essential to survival. However these responses are associated with the rapid erosion of lean tissue, most prominently skeletal muscle. The ability of elderly patients to initiate and sustain appropriate responses to surgical illness may be impaired by alterations in metabolic function and diminished muscle mass, particularly in the face of prolonged or severe stress. The decline in strength associated with advancing age also may be important in the care of elderly surgical patients.^{4,5} Alterations in metabolic response and body composition may contribute to the increased mortality rate associated with elective and emergency surgical procedures, trauma, and sepsis in the elderly.⁶⁻¹¹

The purpose of this study was to determine the effects of age and body composition on the metabolic responses to a specific, controlled stimulus, that is elective colon resection. To minimize the effects of concomitant disease, we chose to study generally healthy, nondiabetic, active, and independent individuals without significant weight loss and with localized disease. To avoid the variability of sex differences in body composition, we studied male patients only.

Patients

Twenty male patients aged 43 to 77 years who were in good general health, active, and independent were studied

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before and after elective colon resection. Patients with diabetes mellitus (fasting serum glucose ≥ 6.1 mmol/L [molar] or hemoglobin A₁ ≥ 0.077) or receiving corticosteroids or adrenergic blocking drugs were excluded, as were patients with carcinoma in whom all identifiable tumor was not resected. A conventional, balanced anesthetic technique was used in all patients, without epidural or high-dose opiate anesthesia.

Methods

The protocol was reviewed and approved by the Research Ethics Committee of the Ottawa Civic Hospital and written, informed consent was obtained from each patient. All patients received similar mechanical and antibiotic bowel preparation and only clear fluids by mouth on the day before surgery. Body weight was measured early on the morning before surgery and vital signs were assessed perioperatively according to nursing routine. Postoperative mobilization and activity were routine. Oral intake was not resumed after operation during the study. Patients had no nitrogen intake during the postoperative study period and received glucose 60 to 150 g/day intravenously in 3.33% or 5% solution, with appropriate electrolytes.

Total body water (TBW) was determined 2 days before surgery, typically the day of admission to hospital, by dilution of ^{18}O -enriched water, in all but the first three patients.¹² Following collection of a baseline urine sample, patients were given an accurately measured quantity (40 to 50 g) of ^{18}O -water orally (1.25 atoms per cent excess; MSD Isotopes, Pointe Claire, Quebec, Canada) late in the evening and fasted overnight. After voiding the next morning, three consecutive urine samples were obtained for later determination of ^{18}O -enrichment by mass spectrometer (SIRA-12, VG Instruments, Greenwich, England) following equilibration with carbon dioxide; TBW was calculated by isotope material balance.

Oxygen consumption and carbon dioxide production were determined at the bedside using a metabolic cart

TABLE 2. *Diagnoses*

Diagnosis	Number of Patients
Carcinoma colon/rectum	12
Diverticular disease	5
Multiple polyps	2
Ulcerative colitis	1

with a canopy and blower system (MMC Horizon System, SensorMedics Corp., Anaheim, CA). Measurements were made on the second afternoon before surgery to familiarize patients with the procedure, and daily at 7 A.M. from the morning of the day before surgery until the third postoperative day, as well as 6 hours after operation. Measurements were made during 10 minutes after a period of equilibration in a quiet, semi-darkened environment. Metabolic rate was calculated as described elsewhere.¹³

Peripheral venous blood was drawn immediately after each of the gas-exchange measurements for determination of white blood cell count, blood urea nitrogen, and serum glucose, insulin, cortisol, and C-reactive protein by standard methods. All urine was collected during serial 24-hour periods from 7 A.M. on the morning of surgery until the third postoperative morning. Urine was analyzed for total nitrogen by pyrochemiluminescence (Nitrogen Analyzer AK-703C, Antek Instrument Corp., Houston, TX), as well as for creatinine and urea nitrogen by standard methods.

Data are presented as mean $\pm$ standard error and were analyzed by paired *t* test, analysis of variance, and multiple linear regression analysis, as indicated, using a microcomputer (Macintosh SE, Apple Computer, Cupertino, CA) and statistical software package (Systat v3.1, Systat Inc., Evanston, IL).

Results

Patient characteristics are summarized in Table 1. Twelve patients underwent resection for malignancy and seven for benign disease (Tables 2 and 3). Preoperative weight loss was absent or minimal, except in a 58-year-

TABLE 1. *Patient Characteristics*

Characteristic	Mean $\pm$ SEM	Range
Patient age (years)	62 $\pm$ 2	43–77
Weight (kg)	76.8 $\pm$ 2.1	58.2–94.5
Height (cm)	178 $\pm$ 1	171–188
Body surface area (M ²)	1.95 $\pm$ 0.03	1.73–2.18
Total body water (kg), n = 17	40.5 $\pm$ 1.1	33.5–48.9
Total body water/body weight, n = 17	0.53 $\pm$ 0.01	0.48–0.60
Duration of operation (minutes)	188 $\pm$ 10	90–285
Postoperative length of stay (days)	10 $\pm$ 1	7–22

TABLE 3. *Surgical Procedures*

Procedure	Number of Patients
Right hemicolectomy	5
Left hemicolectomy	2
Anterior resection rectosigmoid	
Repair colovesical fistula	1
Repair colocolic fistula	1
Small bowel resection	1
Abdominoperineal resection of rectum	1
Abdominal colectomy	3

old patient who had lost approximately 13 kg by history in the preceding year. There was no difference in age or duration of operation between patients with and without malignancy. No variable was related at any time studied to the presence or absence of malignancy or to the duration of operation. Postoperative complications noted were a pelvic abscess, a superficial wound infection, and atelectasis in 43-, 68-, and 55-year-old patients, respectively. Postoperative length of hospital stay was 10 ± 1 days and was not related to age.

Body temperature, white blood cell count, serum cortisol, serum glucose, and serum C-reactive protein all increased after operation, but absolute values and changes with operation were unrelated to patient age (Fig. 1; Table 4). Peak mean values of serum glucose and cortisol and white blood cell count were observed 6 hours after operation, while the maximum body temperature was noted on the first postoperative day and maximum serum C-reactive protein on the following day. Serum insulin concentrations were also increased after surgery, and were highest on the first postoperative morning; serum insulin increased 6 hours after operation was inversely related to age: $298 - 3 \times \text{age}$, $r^2 = 0.29$, $p < 0.05$.

Body weight, body surface area, and TBW (both absolute and as a proportion of body weight) were not related to patient age. Oxygen consumption (VO_2), carbon dioxide production (VCO_2), and metabolic rate (MR) on the morning before and the morning of operation were very similar and were analyzed as the mean of the two determinations (Table 5). Respiratory quotient was lower on the morning of operation compared to the previous morning. Preoperative, resting VO_2 , VCO_2 , and metabolic rate were all strongly related to TBW ($r^2 = 0.54$ to 0.75 , all $p \leq 0.001$) and to patient age ($r^2 = 0.16$ to 0.27 , $p = 0.02$ to 0.08) (Table 6, Fig. 2). Body weight and body surface area were less strongly predictive of preoperative VO_2 (as well as preoperative MR and VCO_2) than was TBW, with coefficients of determination of 0.75 and 0.66 , respectively, for regression equations including age. Mean 24-hour urine creatinine, although determined after operation, was strongly related to resting, preoperative VO_2 ($r^2 = 0.61$, $p < 0.001$), VCO_2 ($r^2 = 0.46$, $p = 0.001$), and MR ($r^2 = 0.61$, $p < 0.001$). When TBW and urine creatinine (expressed in mmol/24 hours) were used as predictors of preoperative VO_2 and MR, then age was not a significant independent variable (Table 6).

Gas-exchange measurements and derived variables determined 6 hours after operation and on postoperative days 1 to 3 were not different by repeated measures analysis of variance and were analyzed as means of the four determinations. Postoperative VO_2 increased 40 ± 5 mL/minute compared to preoperative values ($18 \pm 2\%$, range, 4% to 40%); VCO_2 increased 16 ± 3 mL/minute ($9\% \pm 2\%$; range, -4% to 30%); and metabolic rate increased 10.4

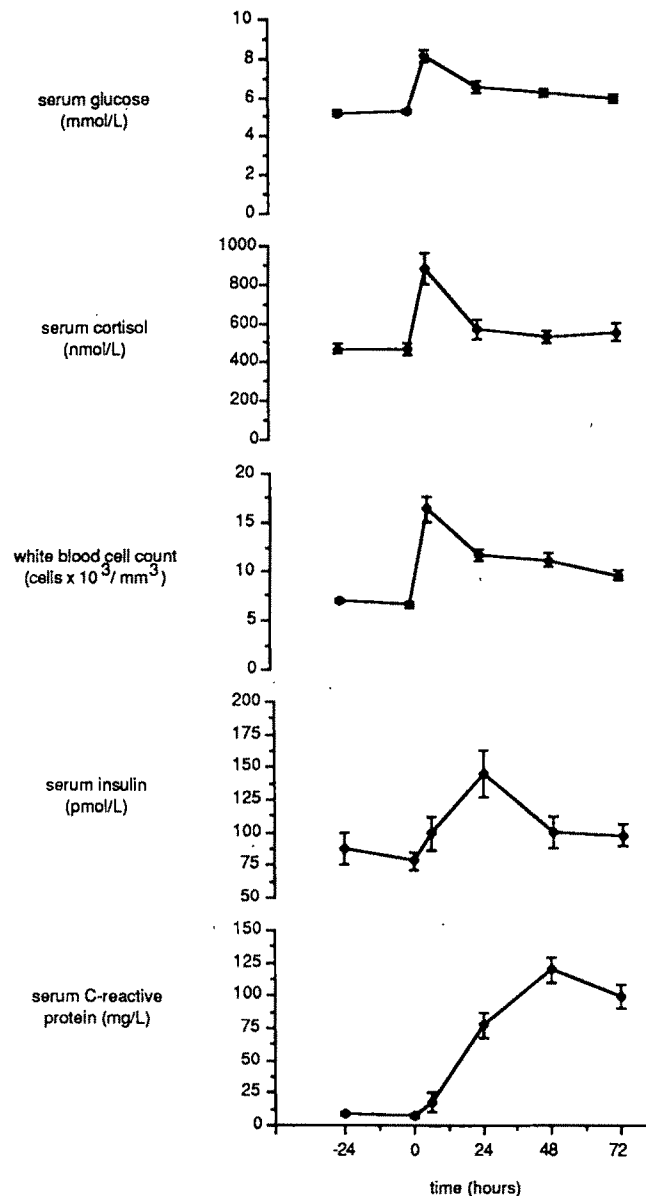


FIG. 1. Changes in peripheral white blood cell count and serum biochemistry after elective colon resection in healthy men aged 43 to 77 years. Time 0 hours = 7 A.M. on the morning of operation.

± 1.3 kcal/hour ($17\% \pm 2\%$; range, 2% to 38%) (Fig. 3). The absolute increases in VO_2 , VCO_2 , and metabolic rate after operation were unrelated to patient age, TBW, 24-hour urine creatinine, or preoperative values; the percentage increases in gas-exchange variables were also unrelated to age, TBW, and urine creatinine.

Similar to the preoperative determinations, postoperative VO_2 , VCO_2 , and MR were dependent on TBW and age; the age coefficients for the pre- and postoperative equations were not significantly different. Postoperative gas exchange values were also correlated with urine creatinine ($r^2 = 0.38$ to 0.44 , all $p < 0.01$). When postop-

TABLE 4. *Temperature, Hematology, and Biochemistry*

	Preoperative		Postoperative			
	Day -1 7 A.M.	Day 0 7 A.M.	Postop. 6 hours	Day 1 7 A.M.	Day 2 7 A.M.	Day 3 7 A.M.
Temperature (rectal,† °C)	36.6 ± 0.1	36.6 ± 0.1	37.1 ± 0.2	37.6* ± 0.1	37.3 ± 0.1	36.9 ± 0.1
White blood cell count (×10 ³ /mm ³)	7.0 ± 0.3	6.6 ± 0.3	16.3* ± 1.4	11.6 ± 0.6	11.1 ± 0.7	9.4 ± 0.5
Serum cortisol (nmol/L)	468 ± 27	463 ± 31	881* ± 82	568 ± 51	528 ± 29	547 ± 44
Serum C-reactive protein (mg/L)	8.6 ± 1.4	8.2 ± 1.5	17.5 ± 7.5	77.3 ± 10.2	119.4* ± 9.6	99.3 ± 9.2
Serum glucose (mmol/L)	5.2 ± 0.2	5.3 ± 0.1	8.1* ± 0.3	6.5 ± 0.3	6.2 ± 0.2	5.9 ± 0.2
Serum insulin (pmol/L)	88 ± 12	78 ± 7	99 ± 13	145* ± 18	100 ± 12	97 ± 8
Blood urea nitrogen (mmol/L)	5.0 ± 0.2	4.4 ± 0.2	4.2 ± 0.4	3.9 ± 0.3	3.5* ± 0.2	3.7 ± 0.3

* $p < 0.01$, values at peak (except BUN, lowest) postoperative time point versus preoperative values (day 0, 7 A.M.), by paired t test.

† Except abdominoperineal resection.

erative gas-exchange values were related to preoperative values (Fig. 4), age and TBW were no longer significant predictors (Table 6). Postoperative respiratory quotient was not dependent on either age or TBW (absolute or as a proportion of body weight).

There was no significant effect of age on 24-hour urine volume, creatinine, urea nitrogen, and total nitrogen on the day of operation and the following 2 days (Table 7), whether expressed in absolute terms or as a function of body weight, TBW, body surface area, or height. Mean daily total urine nitrogen tended to be related to body weight ($r^2 = 0.19$, $p = 0.05$) and to TBW ($r^2 = 0.20$, $p = 0.07$), with similar relationships for urine urea nitrogen but not for urine creatinine. Mean 24-hour urine creatinine was unrelated to urine volume, while total nitrogen and urine volume ($r^2 = 0.30$, $p < 0.05$), and total nitrogen and urine creatinine ($r^2 = 0.36$, $p < 0.01$) were correlated.

Discussion

Lean body mass (LBM) has been observed in several studies to decline predictably in adulthood, accompanied by an increase in body fat and a tendency for body weight to increase.^{14,15} Much of the decrease in lean body mass is accounted for by diminished skeletal muscle mass. Total body water reflects lean body mass because the water content of the LBM is relatively constant and that of fat is minimal.^{16,17} Accordingly TBW tends to decrease with age, both in absolute terms and as a proportion of body weight.¹⁸ The lean body mass is comprised of the extracellular mass and the body cell mass, the latter reflected in intracellular water. The body cell mass (BCM) or cellular mass of the body is defined as 'that component of body composition containing the oxygen-consuming, potassium-rich, glucose-oxidizing, work-performing tissue.'¹⁸ Body cell mass also tends to decline progressively with age, in absolute terms and as a proportion of lean body mass.¹⁸

Age was unrelated to body weight, TBW, and mean 24-hour urine creatinine excretion, suggesting that lean body mass and skeletal muscle mass were not a function of age in the patients studied. However urine creatinine was determined after surgery rather than in an unstressed setting with a controlled diet. Nonetheless creatinine excretion has been observed to be unaltered following the stress of elective hip replacement, although it may increase after severe injury.^{19,20} The requirement that patients be active and independent may have selected older patients in whom LBM, BCM, and muscle mass were preserved. The lack of correlation with age also may reflect the small total number of individuals studied, the relatively limited range of their ages, and the heterogeneity of such age-associated phenomena. Because patients were studied rather than normal subjects, a disease effect on body composition or on the method of determining TBW cannot be excluded, despite the selection of individuals with localized disease and in apparently otherwise good health.

Decreases in lean body mass and body cell mass are thought to account for the decrease in resting oxygen consumption and energy expenditure observed with advancing age.²¹⁻²³ Gregerman²³ observed no effect of age on basal oxygen consumption when expressed as a function of body water, *i.e.*, lean body mass, and Kinney et al.²¹ found a strong relationship between resting oxygen consumption and body cell mass, determined as total exchangeable potassium. The decrease in body cell mass with advancing age is not homogeneous, with muscle mass diminishing more markedly than the viscera.^{14,21,24} Furthermore the metabolic expenditure of different portions of the body cell mass varies considerably, with resting muscle having a relatively small expenditure.²⁵ This would account for the observation of Kinney et al.²¹ that the elderly have a higher energy expenditure per unit body cell mass than do younger individuals. Tzankoff et al.²² measured creatinine excretion in healthy individuals and

concluded that age-related decreases in oxygen consumption were fully attributable to decreases in muscle mass. Thus the finding in the present study that TBW and urine creatinine were the strongest predictors of resting oxygen consumption is consistent with the hypothesis that age-associated changes in resting energy expenditure result from changes in body composition.

Regardless of potential age-associated changes in body composition and preoperative energy expenditure, the changes in oxygen consumption and metabolic rate with operation, expressed in either absolute or proportional terms, were not dependent on age and were similar to findings of other studies of elective abdominal surgery.²⁶ Increased oxygen consumption after tissue injury is thought to be a generalized response involving muscle and the viscera to a comparable extent;²⁷ thus variations with age in the composition of the body cell mass should not result in differences in the increase in energy expenditure with operation.

Serum glucose increased after operation in the presence of normal or increased insulin concentrations; no significant age effect was observed. The occurrence of hyperglycemia, hyperinsulinemia, increased glucose production, and insulin resistance during surgical illness is well recognized.²⁸⁻³⁰ Advancing age, in the unstressed state, has been reported to be accompanied by a minor increase in basal plasma glucose, while tissue sensitivity to insulin diminishes.^{31,32} Thus an exaggeration of the hyperglycemia of stress states would be expected in elderly patients and has been described following blunt trauma.^{33,34} The absence of such an exaggeration after elective surgery may reflect its being a less strong 'stimulus' to metabolic responses. In addition Frayn et al.³⁵ have attributed elevated serum glucose, insulin, and cortisol concentrations in el-

derly trauma patients to limitations in their physical activity. The patients in the present study were all generally active and independent, although no attempt was made to quantitate usual levels of physical activity or to control postoperative activity. The effect of physical activity on carbohydrate metabolism is well recognized and may account in large part for changes associated with aging.³⁶⁻³⁹ Alterations in body composition with age, specifically the loss of skeletal muscle, also presumably reflect long-term physical activity.

The negative nitrogen balance, which follows trauma or surgical operation, is well known and its extent is dependent on the magnitude of the tissue injury, previous nutritional state, and the age and sex of the patient.^{14,19,40} The latter factors are presumed to be relevant in relation to body composition, skeletal muscle mass in particular. That skeletal muscle protein is the predominant source of the excess nitrogen lost is apparent from observed muscle wasting and weakness, associated urinary losses of sulfur and phosphorus, net amino acid efflux from uninjured limbs, and from animal studies of protein turnover in the viscera and carcass.⁴¹⁻⁴³ The findings in the present study that postoperative urinary nitrogen tended to be related to body size (*i.e.*, to body weight and to TBW) and more strongly to urinary creatinine excretion (reflecting muscle mass) are consistent with these concepts. The lack of a constant diet before operation, preoperative mechanical bowel preparation, and differences in postoperative glucose intake and physical activity may each have contributed to variability in postoperative urinary nitrogen.⁴⁴

The initiation and regulation of the metabolic responses to surgical stress is complex and involves classic neuroendocrine pathways as well as the more recently elucidated cytokine mediators. Increased metabolic rate after surgery

TABLE 5. Respiratory Gas-exchange Measurements and Derived Variables

	Gas-exchange Variables			
	Oxygen Consumption (mL/min)	Carbon Dioxide Production (mL/min)	Respiratory Quotient	Metabolic Rate (kcal/hr)
Preoperative†				
Day 1 7 A.M.	228 ± 8	197 ± 7	0.87 ± 0.02	66.3 ± 2.5
Day 0 7 A.M.	227 ± 8	189 ± 6	0.83* ± 0.02	66.0 ± 2.2
Postoperative‡				
Postoperative 6 hours	271 ± 11	209 ± 9	0.77 ± 0.02	77.2 ± 3.2
Day 1 7 A.M.	264 ± 9	204 ± 7	0.77 ± 0.01	75.3 ± 2.6
Day 2 7 A.M.	274 ± 9	213 ± 7	0.77 ± 0.01	78.3 ± 2.5
Day 3 7 A.M.	267 ± 8	207 ± 6	0.77 ± 0.01	76.0 ± 2.2
Mean preoperative	227 ± 8	191 ± 6	—	65.6 ± 2.1
Mean postoperative	267 ± 8	207 ± 6	0.78 ± 0.01	76.1 ± 2.2
Mean change	40 ± 5	16 ± 3	-0.06 ± 0.01	10.4 ± 1.3
Mean % change	18 ± 2	9 ± 2	-7 ± 1	17 ± 2

* $p < 0.05$ versus days before operation by paired t test.

† $p < 0.001$ versus mean preoperative value except respiratory quotient versus preoperative/day of operation.

‡ Postoperative measurements are not different for any variable by analysis of variance.

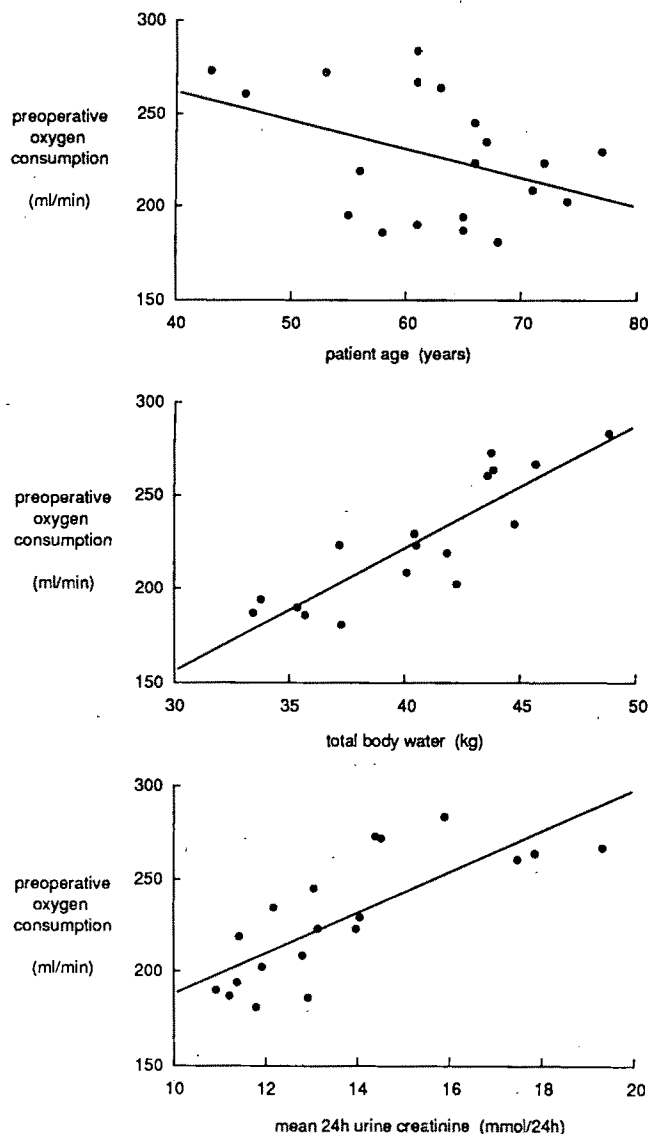


FIG. 2. Effects of TBW, age, and 24-hour urine creatinine on preoperative resting oxygen consumption.

may result from increased elaboration of catabolic or 'stress' hormones, specifically catecholamines, cortisol, and glucagon.^{45,46} Cortisol was the only such hormone

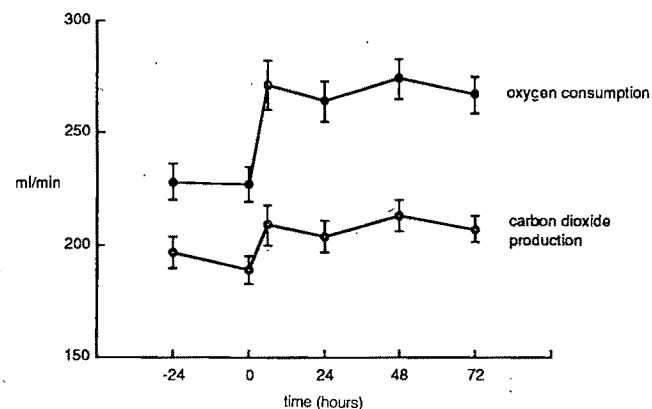


FIG. 3. Pre- and postoperative oxygen consumption and carbon dioxide production. Time 0 hours = 7 A.M. on the morning of operation.

measured; its elaboration (at least as reflected in peripheral circulating concentrations) was short-lived in comparison to the increase in metabolic rate and was unrelated to age. Plasma cortisol had returned almost to preoperative levels by the first morning after operation. Corticosteroid responses have not varied with age in some studies of elective surgical and injured patients,^{26,33,47-49} while in other instances circulating cortisol levels have been observed to be higher in older rather than in younger patients.^{34,35,50} Basal cortisol secretion and clearance are both thought to decrease through adulthood, with the result that plasma concentration is not significantly changed. Regardless of circulating hormone levels, end-organ responses to various hormonal signals are known to be altered with advancing age.^{51,52}

The role of cytokine mediators such as interleukin-1 and tumor necrosis factor is reflected, in part, in the acute-phase response, which includes increased body temperature, accelerated hepatic synthesis of acute phase proteins, and alterations in trace metal distribution. Distinct increases in body temperature, peripheral white blood cell count, and serum C-reactive protein were observed after surgery but none was related to patient age, indicating that acute-phase responses do not vary with age in this model.

TABLE 6. Regression Equations for Respiratory Gas Exchange Variables

Preoperative VO_2 (mL/min) = $31.9 + 6.1 \times \text{TBW}^\ddagger - 0.9 \times \text{age}$ ($p = 0.08$), $r^2 = 0.80^\ddagger$
Preoperative VCO_2 (mL/min) = $99.4 + 3.8 \times \text{TBW}^\ddagger - 1.0 \times \text{age}^*$, $r^2 = 0.66^{**}$
Preoperative MR (kcal/hr) = $13.7 + 1.7 \times \text{TBW}^\ddagger - 0.3 \times \text{age}^*$, $r^2 = 0.82^\ddagger$
Preoperative VO_2 (mL/min) = $-30.9 + 4.4 \times \text{TBW}^\ddagger + 5.6 \times \text{urine creatinine}^*$, $r^2 = 0.85^\ddagger$
Preoperative VCO_2 (mL/min) = $88.3 + 7.5 \times \text{urine creatinine}^\ddagger$, $r^2 = 0.46^\ddagger$
Preoperative MR (kcal/hr) = $-6.2 + 1.2 \times \text{TBW}^\ddagger + 1.6 \times \text{urine creatinine}^\ddagger$, $r^2 = 0.85^\ddagger$
Postoperative VO_2 (mL/min) = $75.0 + 0.8 \times \text{preoperative } \text{VO}_2$, $r^2 = 0.65^\ddagger$
Postoperative VCO_2 (mL/min) = $56.4 + 0.8 \times \text{preoperative } \text{VCO}_2$, $r^2 = 0.68^\ddagger$
Postoperative MR (kcal/hr) = $20.0 + 0.9 \times \text{preoperative MR}$, $r^2 = 0.67^\ddagger$

* $p < 0.05$, $^\ddagger p < 0.01$, $^\ddagger p < 0.001$.

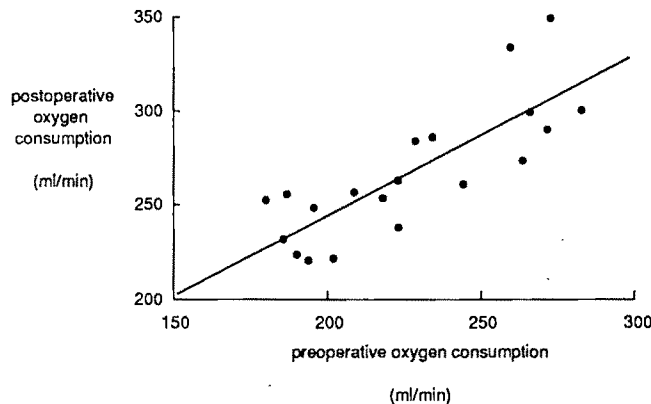


FIG. 4. Relationship between pre- and postoperative oxygen consumption ($r^2 = 0.65$, $p < 0.001$).

The results of this study confirm that preoperative resting energy expenditure is strongly related to body composition; any age effects in the unstressed state are attributable to specific changes in body composition. In addition the metabolic responses of generally healthy men to elective abdominal surgery are not dependent on age. The absence of significant age effects in this study may reflect the magnitude of the stress imposed, the age range of the patients studied, and the selection of active individuals in good general health. Age effects may also have been masked in this study because cross-sectional studies are subject to bias in that older patients, particularly those in good health, are selected by their very survival into old age; cross-sectional studies may demonstrate age 'differences' rather than age 'changes.'¹ Elective colon resection was chosen as a model to allow the study of a moderate surgical stimulus in patients of varying ages who were in otherwise good health, as well as to allow the collection of preoperative control data. Elective procedures carried out in generally healthy individuals of more widely varying ages, such as cholecystectomy or hernia repair, tend to be relatively minor. Thus studies of multiply injured or critically ill patients, patients subjected to a prolonged period of stress, or those with multiple medical illnesses, may demonstrate limitations in the ability of the elderly to initiate and sustain responses comparable to those of younger individuals. Alternatively the intrinsic effects of advancing age on the responses to surgical illness may, indeed, not be substantial once the effects of specific age-

associated diseases and dietary, environmental, and behavioral factors are considered fully.^{36,53} For example postoperative mortality and morbidity rates have been observed to be more strongly related to the number of associated illnesses and American Society of Anesthesiologists physical status than to patient age.^{8,54}

The elderly are a heterogeneous population, reflecting disparate genetic, behavioral, dietary, and environmental influences. The best outcomes from surgical illness in the elderly will be achieved with both an appreciation of the physiologic and pathologic changes that tend to accompany aging, and a careful assessment of the individual patient. Continued improvements in our care of elderly patients will depend, in part, on furthering our understanding of the metabolic responses to surgical stress and how these responses may vary with age.

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TABLE 7. Postoperative Urine Nitrogen (Serial 24 Hour Collections, 7 AM-7 AM)

	Day of Operation	Postoperative Day 1	Postoperative Day 2	Mean
Urine volume (mL/24 hour)	1830 ± 210	2150 ± 190	2260 ± 190	2120 ± 130
Urine creatinine (mmol/24 hour)	13.7 ± 0.7	13.9 ± 0.5	13.5 ± 0.6	13.7 ± 0.6
Urine urea nitrogen (mmol/24 hour)	6.9 ± 0.5	7.6 ± 0.5	7.3 ± 0.7	7.4 ± 0.5
Urine nitrogen (g/24 hour)	8.8 ± 0.7	9.5 ± 0.5	9.1 ± 0.6	9.1 ± 0.5

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Prevention of Postoperative Complications in Jaundiced Rats

Internal Biliary Drainage Versus Oral Lactulose

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In an experiment mimicking a severe surgical trauma by deliberate renal ischemia, the postoperative outcome in jaundiced rats was studied. Intervention studies were performed with preoperative oral lactulose (to reduce endotoxin toxicity) or preoperative internal biliary drainage. Compared to control, obstructive jaundice in rats significantly reduced survival time ($p < 0.001$) and enhanced renal impairment ($p < 0.001$) after renal ischemia. Preoperative supportive therapy of jaundiced rats with oral lactulose increased survival time ($p < 0.01$) but did not reduce deterioration of renal function. Preoperative internal biliary drainage proved to be superior, with a significant reduction of renal impairment ($p < 0.001$) and an improved survival time ($p < 0.001$). Our experiments provide further evidence that obstructive jaundice increases the complication rate following major surgical procedures. Based on our results in rats, we suggest that in obstructive jaundice preoperative internal biliary drainage is the supportive therapy of choice. However, if adequate drainage is not possible, oral treatment with lactulose may help reduce postoperative complications.

SURGERY IN JAUNDICED patients is associated with a mortality rate of approximately 16%.¹ Mortality is, to a large extent, caused by acute renal failure.¹ Clinical and experimental studies indicated that endotoxins play an important role in postoperative complications in obstructive jaundice.²⁻⁵ Furthermore ischemic renal injury is exacerbated by endotoxins⁶ and endotoxemia in combination with ischemic tissue damage results in a high mortality rate.⁷

Preoperative orally administered bile acids or lactulose have been shown to reduce endotoxin toxicity^{8,9} and thus to prevent postoperative complications in jaundiced patients and in rats with experimental biliary obstruction.¹⁰⁻¹³ However both lactulose and bile acids predominantly interfere with endotoxin-related complications whereas other side effects of impaired liver function remain untreated.

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Drainage of the obstructed biliary tract was also suggested as preoperative supportive therapy. However preoperative external biliary drainage did not improve postoperative outcome, as was shown in several prospective clinical trials.¹⁴⁻¹⁶ In a study with rats, internal biliary drainage significantly improved survival after intra-abdominal sepsis.¹⁷ A positive effect of preoperative internal biliary drainage was also suggested in a large clinical study on patients with pancreatic carcinoma.¹⁸ Despite these findings so far, prospective randomized clinical studies confirming these results have not been reported. Furthermore a trial to compare the different supportive therapies was not performed.

In our experiments a model, using bilateral renal ischemia as a severe surgical trauma, was used to study the enhanced complication rate in rats with experimental biliary obstruction. Furthermore the effect of preoperative internal biliary drainage on the outcome of this surgical trauma was compared to the effect of a preoperative anti-endotoxin treatment with oral lactulose. Parameters were nutritional status, renal function, and mortality. Furthermore plasma tumor necrosis factor (TNF), which is a proved mediator of endotoxin toxicity,¹⁹⁻²¹ was measured to evaluate the role of endotoxins in the enhanced morbidity and mortality of surgically treated jaundiced animals.

Materials and Methods

Chemicals and Antibodies

Lactulose (Duphalac) was provided by Duphar (Weesp, The Netherlands). The monoclonal anti-mouse TNF (TN3) was a gift of Drs. Sheehan and Schreiber from Cell-

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tech (Slough, UK).²² The following reagents were purchased: r-murine-TNF and anti-mouse TNF antibodies (Genzyme, Boston, MA), O-phenylenediamine (Sigma Co., St. Louis, MO), peroxidase-conjugated IgG (Jackson, West Grove, PA), bilirubin-kit and triglyceride-kit (Roche, Mijdrecht, The Netherlands), BUN-kit (Bio Merieux, Charbonnières les Bains, France).

Experimental Design

Male Wistar rats (Winkelmann, Borcheln, FRG) weighing 200 to 250 g were used. The rats were allowed free access to water and rat chow. The rats were divided into five experimental groups (Table 1). Control groups consisted of bile duct ligation (BDL), sham operation (SHAM), and bile duct ligation with sham renal ischemia (BDL-SI). The treated groups were (1) bile duct ligation and biliary drainage (BDL-DRAIN), and (2) bile duct ligation and oral lactulose (BDL-LACT). Each group, except the BDL-SI group ($n = 4$), consisted of 10 rats. After 2 weeks all groups, except the BDL-DRAIN group, were exposed to renal ischemia. The BDL-DRAIN group was treated by biliary drainage after 2 weeks and exposed to renal ischemia 3 weeks later. The BDL-LACT group was treated for 3 days with oral lactulose (2 mL 30% lactulose syrup in water) three times per day before renal ischemia. All other groups were given 2 mL saline solution orally using a similar schedule.

Blood was taken by orbital puncture on day 1 and directly before renal ischemia. In the BDL-DRAIN group, blood also was sampled before biliary drainage. Following renal ischemia, blood was sampled after 2 and 4 hours and on days 1, 2, 3, 5, and 7. Body weights of all rats were recorded weekly and on the third day after renal ischemia. Mortality of the rats was recorded during 1 week after renal ischemia; thereafter surviving rats were killed to obtain blood and to take renal biopsies.

TABLE 1. Experimental Design

Day	Bile Duct Ligation				
	Sham	BDL	BDL-SI	BDL-LACT	BDL-DRAIN
Day 1 begin	SHAM	BDL	BDL-SI	BDL-LACT	BDL-DRAIN
Day 11-14 oral	Saline	Saline	Saline	Lactulose	—
Day 14	RI	RI	Sham-RI	RI	Drainage
Day 21	End	End	End	End	—
Day 35	—	—	—	—	RI
Day 42	—	—	—	—	End

BDL, bile duct ligation; SHAM, sham operation; BDL-SI, bile duct ligation and sham renal ischemia; BDL-LACT, bile duct ligation and oral lactulose; BDL-DRAIN, bile duct ligation and internal biliary drainage; RI, renal ischemia.

Surgical Procedures

All surgical procedures were performed under ether anesthesia. Bile duct ligation was performed by ligation of the common bile duct with silk 4-0 sutures, after which it was divided. In the SHAM group the common bile duct was dissected from the hepatoduodenal ligament but was not ligated.

Drainage of the biliary tract was performed by placing a cuffed silastic tube (0.3 mm inner diameter, 0.65 mm outer diameter) in the dilated common bile duct, which was inserted in the duodenum through a small stab wound. To prevent leakage the duodenum was fixed on the common bile duct with three 6.0 silk sutures. Technical failure caused biliary leakage and death in five rats. These rats were excluded from the study.

Renal ischemia was performed in all rats except the BDL-SI group. The entire renal pedicle was dissected and clamped on both sides. In the BDL-SI group, the renal pedicle was dissected but not clamped. After control of vascular occlusion, the abdomen was closed and the rats were allowed to awake. Rats were kept under an infrared lamp to maintain a constant body temperature. After 45 minutes the occlusion clamps were removed. Reperfusion of the kidneys was checked macroscopically.

Laboratory Tests

All determinations were performed with a Cobas Bio (Hoffman La Roche, Basel, Switzerland). Albumin was measured as described.²³ Blood urea nitrogen (BUN) was determined in all blood samples. Bilirubin levels were determined in blood samples of day 1, before, and on day 7 after renal ischemia. Albumin levels were determined on days 1 and 7, 1 day before, and 3 and 7 days after renal ischemia. Plasma triglycerides and TNF were determined on day 1, before renal ischemia, and 2 hours, 4 hours, and 1, 2, 3, 5, and 7 days after renal ischemia. TNF was measured with a sandwich enzyme-linked immunosorbent assay (ELISA), as described previously.²⁴ Tumor necrosis factor levels of the samples were determined by calculation against a standard curve obtained with a serial dilution of recombinant murine TNF. All samples were measured in duplicate. The lower detection limit of the ELISA was approximately 150 pg TNF/mL.

Determination of Ischemic Damage to the Kidneys

Renal biopsies were obtained within 12 hours of death or immediately after the rats were killed. Biopsies were snap frozen in liquid nitrogen. Frozen tissue was postfixed in 4% buffered formalin. Histologic examination was performed double blind using a qualitative grading system. Tubular regeneration was considered present if anisonucleosis or increased mitotic activity was observed.

Statistical Analysis

Student's *t* test for unpaired data was used for statistical analysis. Results are expressed as mean $\pm$ SD, unless otherwise indicated. *P* values less than 0.05 were considered statistically significant.

Results

Experimental Biliary Obstruction Enhances Mortality and Morbidity After Renal Ischemia in Rats

The increased susceptibility of jaundiced rats to postoperative complications was studied by subjecting rats with experimental biliary obstruction to renal ischemia. Both BDL and BDL-SI rats were deeply jaundiced after 2 weeks (Table 2). The nutritional parameters, body weight and serum albumin, were not different in the BDL and BDL-SI rats 2 weeks after bile duct ligation. Compared to SHAM rats, a significant weight loss was observed in the jaundiced rats 1 week after bile duct ligation, which partly recovered during the second week (Fig. 1). Two weeks after bile duct ligation, serum albumin levels were significantly lower in BDL and BDL-SI rats compared to SHAM ($p < 0.001$) (Table 3). Renal ischemia induced a dramatic weight loss and a reduction of serum albumin in all experimental groups. No significant difference between SHAM, BDL and BDL-SI was observed.

After renal ischemia SHAM rats showed a sharp increase in BUN levels, which recovered after 1 to 3 days (Fig. 2). In BDL rats increase of BUN was significantly higher during the first 24 hours (change of BUN in mmol/L [molar]: SHAM 41.6 ± 6.7 versus BDL 54.7 ± 4.2 , $p < 0.001$). Thereafter BUN in BDL rats did not recover but increased. Sham ischemia in BDL-SI rats did not affect BUN (data not given).

Mortality after renal ischemia was recorded during 7 days; thereafter remaining rats were killed (Fig. 3). Fol-

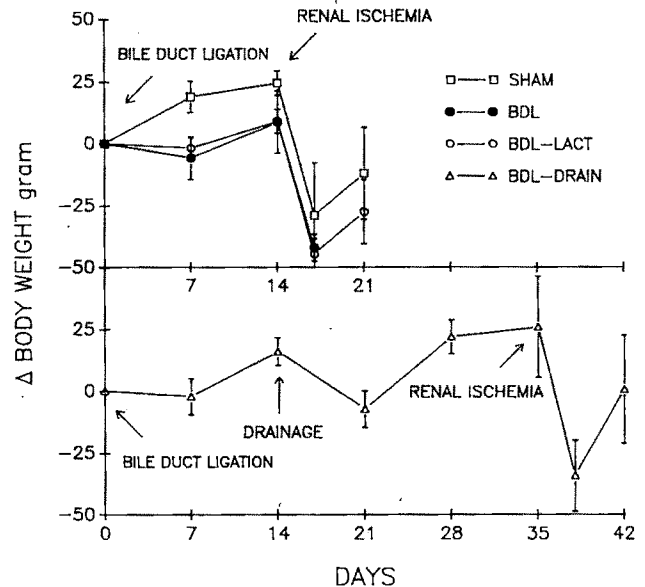


FIG. 1. Changes of body weight of the rats during the experiments in the different experimental groups. Body weight of each individual rat was recorded weekly. Values shown are mean $\pm$ SD. In the upper part, weight changes of SHAM, BDL, and BDL-LACT rats are shown. In the lower part, weight changes of BDL-DRAIN rats before and after internal biliary drainage are presented.

lowing renal ischemia in SHAM rats, 4 of 10 rats died, resulting in a survival time of 134 ± 49 hours. No BDL rat survived after renal ischemia; the survival time of 54 ± 35 hours was significantly lower compared to SHAM rats ($p < 0.001$). BDL-SI rats all survived the 7-day observation period after sham renal ischemia.

Preoperative Supportive Therapy Reduces the Occurrence of Postoperative Complications

Following bile duct ligation, changes of bilirubin levels (Table 2), serum albumin (Table 3), and body weight (Fig.

TABLE 2. Serum Bilirubin Levels in Bile Duct Ligated Rats

Group	Begin	Drainage	RI	End
SHAM	2.6 ± 0.5	—	2.4 ± 0.7	$n = 6$ 3.2 ± 0.2
BDL	2.6 ± 0.5	—	117 ± 39	$n = 0$ —
BDL-SI	$n = 4$ 2.8 ± 0.5	—	$n = 4$ 101 ± 37	$n = 4$ 60 ± 19
BDL-LACT	2.5 ± 1.0	—	132 ± 23	$n = 4$ 208 ± 55
BDL-DRAIN	2.7 ± 0.6	114 ± 22	2.5 ± 0.5	$n = 9$ 2.8 ± 0.8

Bilirubin levels are given in $\mu\text{mol/L}$ and are the mean $\pm$ SD of 10 rats, unless indicated in the table. Exact timetable of the different observation points in each individual experimental group is given in Table 1 (RI, renal ischemia).

TABLE 3. Serum Albumin Levels During the Experiments

Group	Begin	Drainage	RI	End
SHAM	32.0 ± 1.7	—	34.0 ± 1.3	$n = 6$ 30.9 ± 1.2
BDL	32.2 ± 1.0	—	28.0 ± 1.7	$n = 0$ —
BDL-SI	$n = 4$ 31.2 ± 1.8	—	$n = 4$ 25.9 ± 0.7	$n = 4$ 23.4 ± 1.4
BDL-LACT	32.9 ± 1.0	—	28.6 ± 1.5	$n = 4$ 25.2 ± 0.9
BDL-DRAIN	31.6 ± 2.0	27.8 ± 1.4	30.7 ± 2.8	$n = 9$ 29.7 ± 3.0

Plasma albumin levels (in g/L) are mean $\pm$ SD. All groups consisted of 10 rats unless indicated in the table. Significant differences are given in Results. Exact timetable of the various observation points in each individual experimental group is given in Table 1 (RI, renal ischemia).

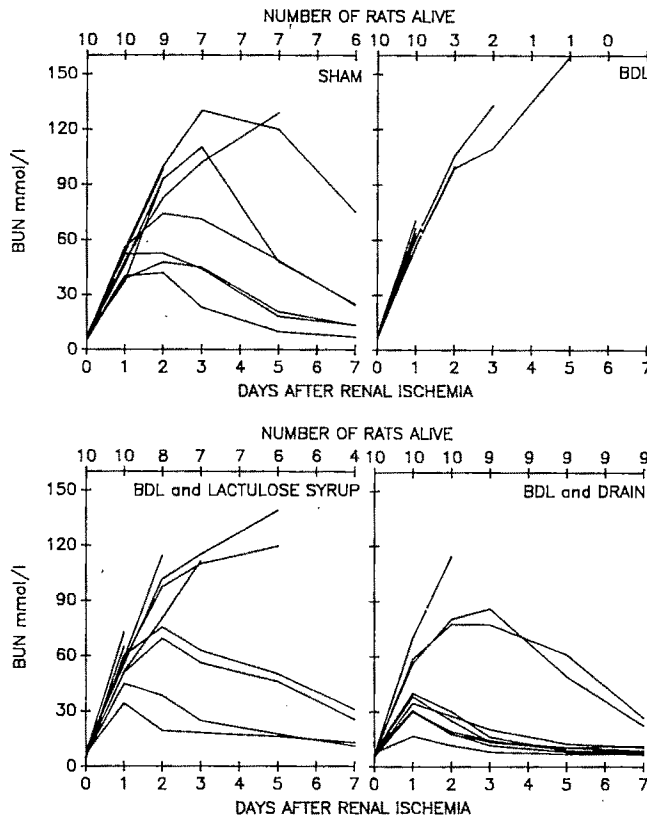


FIG. 2. Renal function after bilateral renal ischemia in jaundiced rats; effect of intervention with lactulose and internal biliary drainage. Blood urea nitrogen levels of each individual rat after bilateral renal ischemia are shown. The upper x-axis displays the number of surviving rats. The different graphs show the results of different experimental groups. The results of the BDL-SI rats are not given because, after sham renal ischemia, BUN levels remained unaltered.

1) of BDL-LACT and BDL-DRAIN rats were not significantly different from BDL rats. Internal biliary drainage resulted in a rapid decrease of clinical jaundice and after 3 weeks bilirubin levels returned to normal (Table 2).

Lactulose treatment affected neither serum albumin nor body weight (Fig. 1, Table 3). In contrast internal biliary drainage significantly improved nutritional status. Body weight dropped during the first week after drainage; thereafter weight gain was similar to that of SHAM rats (Fig. 1). Albumin levels recovered completely 3 weeks after biliary drainage (Table 3).

Lactulose treatment did not significantly reduce deterioration of renal function after renal ischemia (change of BUN in mmol/L: BDL-LACT 47.8 ± 12.6 versus BDL 54.7 ± 4.2 , not significant) (Fig. 2). However renal impairment in BDL rats was significantly different from SHAM rats, whereas changes of BUN in BDL-LACT rats were not (change of BUN in mmol/L: BDL-LACT 47.8 ± 12.6 versus SHAM 41.6 ± 4.7 , not significant). Internal biliary drainage resulted in a significantly reduced renal impairment compared to both BDL and BDL-LACT rats

(change of BUN mmol/L: BDL-DRAIN 34.0 ± 15.6 mmol/L versus BDL, $p < 0.001$; BDL-DRAIN versus BDL-LACT, $p < 0.05$) (Fig. 2). Change of BUN in BDL-DRAIN was not significantly different from SHAM rats.

In contrast to renal function, lactulose treatment of BDL rats significantly improved survival time after renal ischemia (BDL-LACT 125 ± 53 hours versus BDL 54 ± 35 hours, $p < 0.01$) (Fig. 3). Furthermore survival time of BDL-LACT rats was not significantly different from SHAM rats. Survival time in rats with internal biliary drainage showed a highly significant increase compared to BDL rats (BDL-DRAIN 156 ± 35 hours versus 54 ± 35 hours, $p < 0.001$), and was not significantly different from BDL-LACT and SHAM rats (Fig. 3).

Relation of TNF and Triglycerides to Postoperative Complications in Jaundiced Rats

Plasma TNF measurements were performed to study the role of endotoxin in occurrence of complications. The mediator of endotoxin toxicity TNF was measured rather than endotoxin itself because plasma endotoxin determinations are difficult and, most importantly, because *in vivo* plasma endotoxin appears intermittent, making single daily samples unreliable.

Substantial amounts of TNF were found in plasma from BDL and BDL-LACT rats following renal ischemia (Table 4). In plasma from SHAM, BDL-SI, and BDL-DRAIN rats, no detectable TNF was measured. Plasma TNF levels did not correlate with mortality.

Plasma triglyceride levels were determined to further study the role of endotoxins in postoperative complications in jaundiced rats. In SHAM, BDL-SI, and BDL-

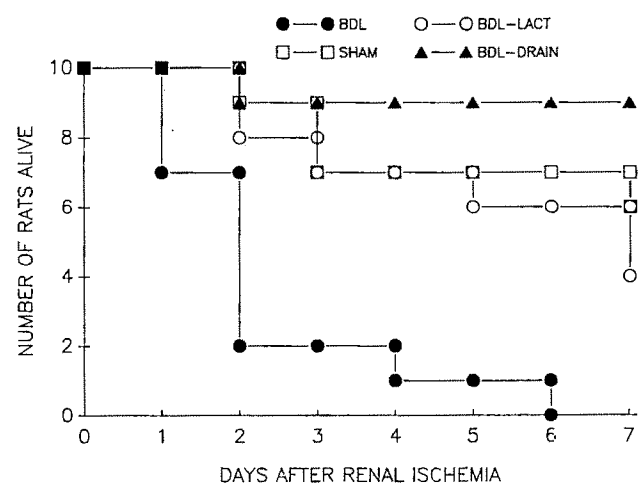


FIG. 3. Survival of rats after a severe surgical trauma, effect of preoperative treatment. After renal ischemia survival was observed during 7 days. Thereafter remaining rats were killed. Preoperative treatment consisted of oral lactulose during 3 days before the trauma in the BDL-LACT group or internal biliary drainage 3 weeks before renal ischemia in the BDL-DRAIN group.

TABLE 4. Plasma TNF Levels After Renal Ischemia

Group	SHAM	BDL	BDL-SI	BDL-LACT	BDL-DRAIN
Rat					
1	—*	3350*	—	—*	—*
2	—*	—*	—	1038*	—
3	677*	—*	—	220*	—
4	—	—*	—	640	—
5	—	230*	—	—	—
6	—	—*	—	557*	—
7	—	569*	—	590*	—
8	—*	2120*	—	—	—
9	—	—*	—	—*	—
10	—	—*	—	8263	—

Plasma TNF levels were measured with an ELISA and are expressed in pg/mL. Values are the average of duplicate determinations. The highest TNF values of each individual rat after renal ischemia are shown. Rats that died are marked with an asterisk.

DRAIN rats, triglyceride levels remained within the normal range. After renal ischemia in BDL rats, a significant increase in triglyceride levels was observed (Fig. 4). Triglyceride levels of surviving BDL-LACT rats were significantly lower compared to deceased BDL-LACT rats (3.6 ± 0.6 mmol/L versus 5.9 ± 0.6 mmol/L, $p < 0.001$). Furthermore mean plasma triglyceride levels of surviving jaundiced rats (from the BDL-LACT and BDL-SI groups) were significantly lower compared to plasma triglyceride levels from jaundiced rats that died (from the BDL and BDL-LACT groups) (surviving jaundiced rats 2.8 ± 0.9 mmol/L versus deceased jaundiced rats 5.9 ± 1.3 mmol/L, $p < 0.001$).

Renal Histology

Differences in the grade of ischemic damage between the left and the right kidney of each rat were not observed, indicating that vascular occlusion was effective. Bile duct ligation rats showed severe cortical necrosis. Biopsies from BDL-SI rats were normal. Renal tissue from deceased SHAM, BDL-LACT, and BDL-DRAIN rats showed moderate to severe cortical necrosis and, in most samples, signs of tubular regeneration. In surviving SHAM, BDL-LACT, and BDL-DRAIN rats, cortical necrosis was moderate or absent with or without signs of tubular regeneration.

Discussion

In our experiments bilateral renal ischemia was used as a severe surgical trauma to study postoperative morbidity and mortality in rats with obstructive jaundice. In BDL rats renal impairment was significantly increased and survival time was significantly decreased compared to SHAM rats following renal ischemia. These results are supported by previous experimental studies in which ob-

structive jaundice in rats significantly increased mortality after intra-abdominal sepsis¹⁷ and after renal ischemia.^{25,26}

We also found that experimental biliary obstruction caused a decrease of serum albumin, which correlates with the results of previous studies in rats.^{5,27} Low serum albumin levels were associated with a high complication rate in several studies of risk factors related to postoperative outcome in jaundiced patients.²⁸⁻³⁰

Besides low serum albumin, gut-derived endotoxins were suggested to play an important role in the occurrence of complications in patients with obstructive jaundice.^{2-4,10} In a previous study, however, we could not measure substantial amounts of endotoxin in plasma of jaundiced rats.⁵ Nevertheless a clear relation was shown between endotoxin and suppression of cellular immunity.⁵

Endotoxin toxicity is mainly mediated by TNF^{20,21}, therefore we studied plasma TNF levels of all rats in our experiments. However, like endotoxin measurements, plasma TNF determinations *in vivo* were very difficult and unpredictable. Tumor necrosis factor has a very short half-life time and it was found that in patients treated with continuous infusions of TNF the previously measured plasma TNF levels disappeared, despite clinical evidence of its effects.²¹

One of the clinical effects of TNF is the inhibition of lipoprotein lipase, resulting in a hypertriglyceremia.³¹ Furthermore it was shown recently that TNF stimulates a *de novo* synthesis of triglycerides in the liver.³² Because plasma triglycerides remain elevated for at least 17 hours after TNF stimulation,³² they offer an indirect way to further study the possible involvement of endotoxins and/or TNF.

In our experiments serum TNF measurements could not confirm the role of endotoxins in the observed mor-

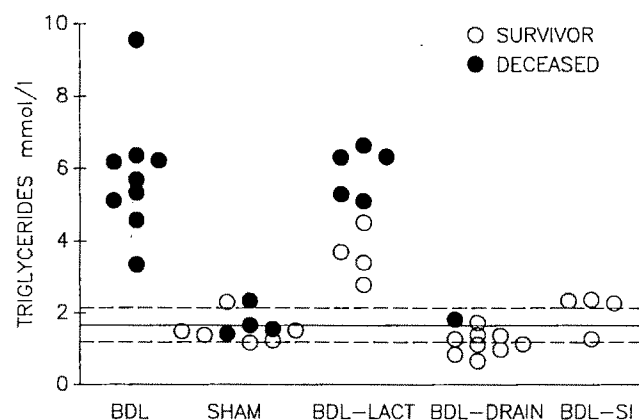


FIG. 4. Correlation of serum triglycerides with mortality in jaundiced rats. Triglycerides were measured in all rats as an indirect parameter of TNF activity and consequently of endotoxin toxicity. The highest triglyceride level of each rat after renal ischemia is shown. The BDL-SI group underwent sham renal ischemia. Solid line and dashed line represent mean $\pm$ SD of triglyceride levels in control rats.

bidity and mortality after renal ischemia. Only in jaundiced rats could substantial amounts of TNF be measured, and no correlation was found between TNF levels and mortality. However, after renal ischemia in jaundiced rats, a highly significant relation between raised serum triglyceride levels and mortality was found. This suggests that TNF, and consequently endotoxin, may be involved.

The effect of most clinically used preoperative treatments to prevent complications in jaundiced patients are still disappointing.¹ Intravenous mannitol was suggested to prevent postoperative renal complications; however the results of early studies on mannitol have been recently disputed.^{25,26,33} Preoperative external biliary drainage after initial hopeful reports³⁴⁻³⁶ also was found to be ineffective.¹⁴⁻¹⁶ In our experiments preoperative intervention with lactulose or internal biliary drainage significantly reduced postoperative complications in jaundiced rats.

Lactulose significantly increased survival time after renal ischemia. Lactulose treatment, however, did not improve liver function or nutritional status. In previous studies it was suggested that lactulose was effective by inactivating endotoxin¹³ or by reducing the release of its mediator TNF.⁸ The relation of serum triglycerides (reflecting TNF activity) and postoperative mortality in jaundiced rats, as observed in our study, further supports the hypothesis that lactulose reduces endotoxin toxicity.

Internal biliary drainage not only significantly increased postoperative survival time but also significantly reduced renal impairment after renal ischemia. An explanation of the difference with lactulose treatment could be that internal biliary drainage not only re-established bile flow to the intestine, thus reducing endotoxin toxicity, but also improved liver function and nutritional status. Reduction of endotoxin toxicity is probably the effect of bile acids present in bile, as was suggested by several clinical studies¹⁰⁻¹² and by our results in an *in vitro* study in which bile acids reduced endotoxin-induced TNF production by monocytes.⁹

The good results of internal biliary drainage accord with the observation by Trede et al.¹⁸ that preoperative internal biliary drainage decreased postoperative complications in patients with pancreatic carcinoma. However drainage-related complications were not reported and safety of the internal drainage procedure must be proved. Furthermore biliary drainage must last for at least several weeks, as was reported previously.³⁷

We suggest, although the efficacy in patients must be determined, that internal biliary drainage is the preoperative supportive therapy of choice in obstructive jaundice. However adequate drainage of the entire biliary tract is not always possible and in some patients surgical treatment is acutely indicated. In these instances short-term preoperative treatment with oral lactulose may improve postoperative outcome.

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Effects of Oxygen Supply on Protein Metabolism in Surgically Injured Rats

Oxygen as a Nutrient

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The effect of various inspired oxygen concentrations on protein metabolism after surgery was investigated in rats. Surgical injury was produced by transecting the stomach. Rats were divided into three groups, *i.e.*, a hyperoxic group, a hypoxic group, and a normoxic control group, which were supplied with 40%, 10%, and 21% oxygen, respectively, for 7 days after operation. All rats were fed intravenously (257 kcal/kg/day, kcal/N: 185.5) and whole-body protein turnover was measured using the constant infusion of ^{15}N glycine technique developed by Picou and Taylor-Roberts. For six days after operation, the cumulative nitrogen balance was negative for the hypoxic rats, while hyperoxic rats showed a positive balance that was significantly higher than in control rats ($p < 0.01$). Protein synthesis and breakdown rates increased markedly and the rate of synthesis exceeded that of breakdown in the hyperoxic group, but in the hypoxic group synthesis remained unchanged while breakdown increased moderately. These results indicate that oxygen, as a nutrient, is effective for improving postoperative protein metabolism.

A LARGE AMOUNT of the free energy derived from food is used to efficiently produce adenosine triphosphate (ATP) through oxidative phosphorylation and the continual resynthesis of ATP is necessary to maintain normal body functions. In the postoperative course of gastrointestinal surgery, however, the supply of oxygen to the tissues is often impaired due to low-flow states or pulmonary complications.¹⁻³ Many patients who undergo abdominal surgery experience arterial hypoxemia for several days after surgery, even in the absence of pulmonary complications. Oxygen therapy is, therefore, commonly prescribed for those with postoperative hypoxemia. There is very little information available on the correlation between various inspired oxygen concentrations and postoperative protein metabolism. The physiologic effects of hypoxia and hyperoxia have been investigated primarily in subjects that were fed *ad libitum* under either hypobaric or hyperbaric conditions.

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The present study was designed to examine the effect of inspired oxygen concentrations on postoperative protein metabolism under normobaric conditions. The experiments were performed in surgically injured rats that received definite amounts of nutrients intravenously to avoid any possible confounding effects of oxygen concentrations and/or atmospheric pressure on protein intake due to changes in appetite. To assess protein metabolism, we measured whole-body protein turnover using the ^{15}N glycine constant infusion method. Nitrogen balance was also examined.

Materials and Methods

Animal Treatment

The animals used in the present study were treated in accordance with authors' institution's guidelines for the care of laboratory animals.

Thirty male Wistar rats weighing 200 g each were acclimated to constant laboratory conditions for at least 7 days before use in the experiments and were fed rat chow *ad libitum*. Each rat was anesthetized by intraperitoneal injection of sodium pentobarbital (5 mg/100 g body weight). The forestomach was transected and immediately repaired by continuous sutures with 6-0 nylon thread. A silastic catheter (inner diameter, 0.5 mm; outer diameter, 1.0 mm) was implanted in the superior vena cava and intravenous infusion was started immediately. The rats were caged individually in specially equipped glass chambers (Sugiyamagen, MC-AP, 298 cm² × 30 cm, 8.5 L, Tokyo, Japan) and exposed to different fractions of inspired oxygen (FiO_2) under normobaric conditions for a period of 7 days.

On the day of surgery, each rat received nutrients intravenously (121 kcal/kg/day, kcal/N: 110). During the next 6 days, each rat was fed full isocaloric (257 kcal/kg/day), isonitrogenous (1218 mgN/kg/day) intravenous solutions containing adequate and identical mineral and vitamin supplements (Table 1). Twenty-one per cent of the nonprotein energy was given as soybean oil emulsion (Intrafat, Nihon-Seiyaku, Tokyo, Japan) and the solutions were infused continuously using a peristaltic pump (502S, Watson-Marlow, Falmouth, England).

Exposure to Various Oxygen Concentrations

The rats were divided into three groups of 10 rats each, *i.e.*, a hyperoxic group ($F_{IO_2} = 0.40$, $n = 10$), a hypoxic group ($F_{IO_2} = 0.10$, $n = 10$), and a control group ($F_{IO_2} = 0.21$, $n = 10$).

Hyperoxic and hypoxic breathing mixtures were prepared by combining oxygen and nitrogen gas to achieve and maintain the designated concentration, which was continuously monitored in the chamber. The gas mixture was fed into the chamber at a rate of 250 mL/minute. Expired gas was collected using a water-sealed system (Fig. 1). The control rats were kept in open chambers and breathed atmospheric air.

Isotope Administration

The whole-body protein turnover was estimated from the urinary ^{15}N enrichment at plateau using the constant isotope infusion method of Picou and Taylor-Roberts.⁴

On the sixth postoperative day, 70 to 80 mg of ^{15}N glycine (corresponding to 51 to 87 mg ^{15}N /kg/day) was added to the infusate, which was given constantly for a period of 30 to 33 hours. The ^{15}N glycine solution was prepared and sterilized in the author's pharmaceutical department from commercial ^{15}N glycine (99 atom percentage excess, ICN Biomedical, Inc., Cambridge, MA).

TABLE 1. Composition of TPN Solution (day^{-1})

Component	Amount
Glucose (g/kg)	39.0
Fat (g/kg)	6.0
Amino acids (g/kg)	7.8
Energy (kcal/kg)	257.0
kcal/N	185.5
Vitamine A (I.U.)	1250
B ₁ (mg)	6.25
B ₂ (mg)	1.25
B ₆ (mg)	1.88
C (mg)	62.5
D ₂ (I.U.)	125
E (mg)	0.63
Nicotinamide (mg)	12.5
Pantotheine (mg)	3.13

TPN, total parenteral nutrition

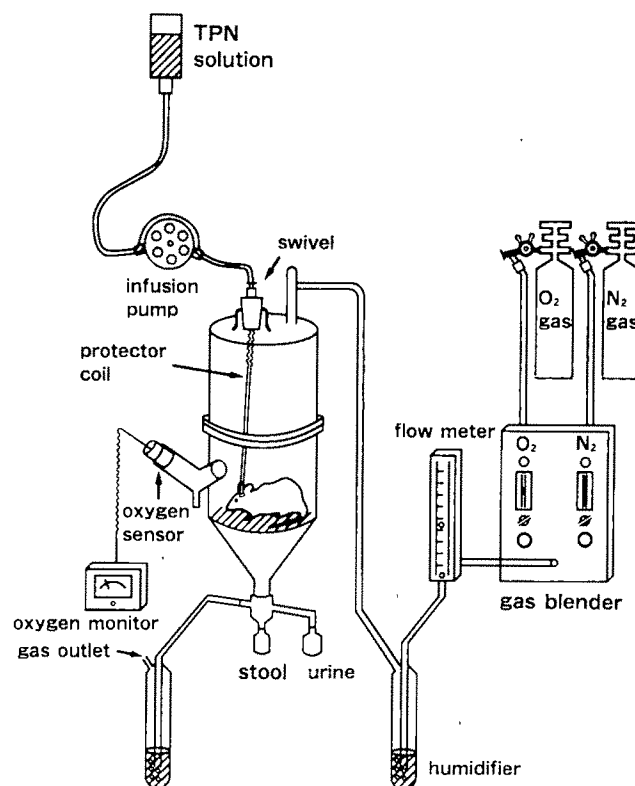


FIG. 1. Experimental apparatus.

Sample Collection and Analysis

Timed urine samples were taken during the isotopic study to detect the plateau value. Total urinary nitrogen was used as urinary end product. These samples were digested using the Kjeldahl analysis and the resulting ammonia was steam-distilled into dilute hydrochloric acid and converted into nitrogenous gas using lithium hypobromite. The hypobromite reaction was performed in an initial vacuum of 1.3×10^{-2} Pa. Urinary ^{15}N enrichment was measured on a mass spectrometer (Hitachi, RMI-2, Tokyo, Japan) and was expressed as an atom percentage excess relative to a comparable sample obtained from each subject before the infusion.

Daily urine specimens were also collected and analyzed for total nitrogen using the micro-Kjeldahl analysis. All rats were weighed at the beginning of the experiment and at 7-day intervals thereafter for the duration of the study.

Data Analysis

The Dunnett multi-variate *t* test was used for the statistical analyses. Differences were considered significant at a *p* value of less than 0.05. All values are represented as means $\pm$ SD.

Results

Body Weight

Different concentrations of inspired oxygen resulted in significantly different body weights (Table 2). The body weight gain in hyperoxic rats was $6.3\% \pm 3.1\%$ of their initial body weight, whereas a marked loss of body weight of $-6.8\% \pm 2.0\%$ was observed in hypoxic rats.

Nitrogen Balance

Figure 2 shows the results of the cumulative nitrogen balance study on the third and sixth postoperative days. Hypoxic rats showed a negative cumulative balance for 6 days (-81.2 ± 53.9 mgN/100 g), whereas hyperoxic rats had a significantly higher positive balance for the same time frame (230.8 ± 60.8 mgN/100 g) than control rats (106.4 ± 89.9 mgN/100 g). Similar significant differences were noted in the cumulative nitrogen balance for the first 3 postoperative days. Figure 3 shows the daily nitrogen balance curves for each group. The poor negative nitrogen balance of the hypoxic group and the significant difference between it and the control group that was observed on the first postoperative day was found to persist throughout the 6 days of the study. In the hyperoxic group, the better nitrogen balance relative to the control group continued until the fourth postoperative day.

Time Course of ^{15}N Enrichment

Figure 4 shows the curves of ^{15}N specific activity in total urinary nitrogen following intravenous infusion of ^{15}N glycine. The data shown are from three to four individual rats from each group. The time to the plateau was different between the control group and the other two groups. A plateau was reached in both hyperoxic and hypoxic rats in 23 to 30 hours, while a plateau in the control group data was not seen until 30 hours.

TABLE 2. Effect of Oxygen Concentration on Body Weight

Group	Preoperative g	7 th POD g	Variation rate* %
Hyperoxic (10)†	189.0 $\pm$ 13.5	200.6 $\pm$ 10.9	6.3 $\pm$ 3.1†
Hypoxic (10)	197.8 $\pm$ 8.1	184.3 $\pm$ 7.6	-6.8 $\pm$ 2.0‡
Control (10)	197.9 $\pm$ 7.6	201.7 $\pm$ 8.3	1.9 $\pm$ 2.8

A gain in body weight was observed in both the hyperoxic and control groups, while the hypoxic group showed a loss in body weight. All values are mean $\pm$ SD.

* Percentage change from preoperative weight.

† The numbers in parentheses are the numbers of rats used.

‡ Significant difference from the control group ($p < 0.05$).
POD, postoperative day.

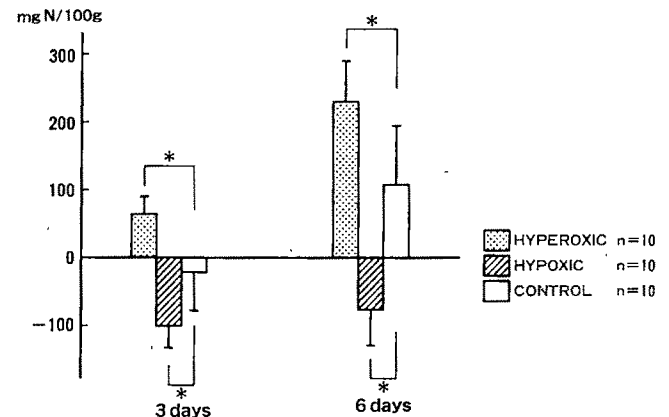


FIG. 2. Cumulative nitrogen balance: hyperoxic rats are positive at 3 days, whereas hypoxic rats continued to have a negative cumulative nitrogen balance even at 6 days. Data are presented as mean $\pm$ SD. *Significant difference from the control group ($p < 0.01$).

Whole-body Protein Turnover

The results of the analyses of whole-body protein turnover are shown in Tables 3 and 4. The whole-body protein turnover rate was highest in the hyperoxic group and lowest in the control group. The nitrogen balance of the hyperoxic group was not statistically different from that of the control group on the sixth postoperative day (Fig. 3); however significant increases in the rates of both protein synthesis and breakdown in the dynamic study of nitrogen turnover were seen during the same period. The rate of protein synthesis was found to exceed that of the breakdown. Hypoxic rats that had a depressed nitrogen balance on the sixth postoperative day (Fig. 3) showed a moderately increased rate of protein breakdown and an un-

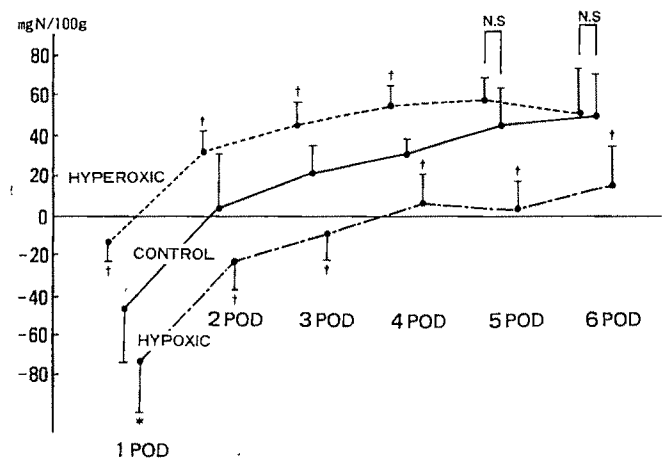


FIG. 3. Daily nitrogen balance study curves: hyperoxic and hypoxic rats are paralleled but remained significantly different from the control rats, except for the hyperoxic group on days 5 and 6 after operation. Data are presented as mean $\pm$ SD. *Significant difference from the control group ($p < 0.05$). †Significant difference from the control group ($p < 0.01$).

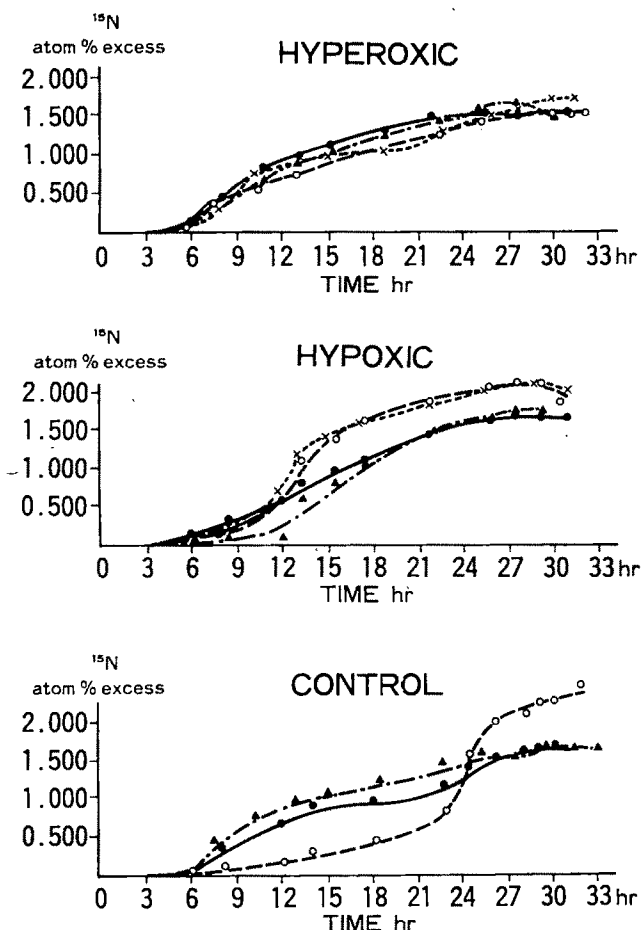


FIG. 4. ^{15}N -specific activity curves in total urinary nitrogen after constant infusion of 99 atom % ^{15}N -glycine. The plateau is between 23 and 30 hours in the hyperoxic and the hypoxic rats and at least 30 hours in the control group.

changed rate of protein synthesis in the isotopic study during the same period (Tables 3 and 4).

Discussion

Continuous infusion of ^{15}N -labeled amino acids has been used in studies of the dynamic aspects of body protein metabolism in humans^{4,5} and laboratory animals^{6,7} and considered to be more applicable to comparative processes.⁸

The proper identification of a plateau in urinary ^{15}N enrichment, which implies an isotopic steady state in the assumed amino acid pool, is vital to making accurate calculations of protein turnover. There have been few reports in the literature showing the ^{15}N enrichment curve to the plateau level in rats. We collected timed urine samples during a period of more than 30 hours to elucidate the time course of ^{15}N enrichment to a plateau level. Stein et al.^{6,7} used the last 1 to 2 hours of urine after 18 to 20 hours as the plateau values in their measurements without showing the entire curve.

Hypoxemia and depressed pulmonary function are commonly observed in patients during the first few days after abdominal surgery,¹⁻³ and oxygen therapy has been used to relieve the hypoxic condition. Very few reports on the relationship between oxygen supply and the postoperative nutritional state have been published. In the present study it was assumed that the metabolic changes in the control rats were an indication of the physiologic response of recovery from surgical stress and that the results obtained from both the hyperoxic and hypoxic groups reflect the effect of oxygen supply on protein metabolism in early postoperative days.

Protein metabolism under hypoxic conditions has been studied mainly as it relates to high-altitude physiology. High-altitude hypoxia can be characterized best as hypobaric hypoxia, which is associated with a loss of body weight in humans and in small laboratory animals, retarded growth rates,⁹ depressed rates of protein synthesis,¹⁰ elevated rates of protein degradation,¹¹ and negative nitrogen balances.¹² In the present study, the animal subjects were given definite amounts of nutrients through total parenteral nutrition to eliminate the hypoxic effects on the alimentary tract (e.g., reducing appetite, impairing digestion and absorption)^{9,13} and normobaric hypoxia was used to eliminate the effects of low atmospheric pressure.

The results demonstrated that following abdominal surgery, oxygen-deficient rats lost body weight, had a depressed nitrogen balance, an accelerated rate of protein breakdown, and an unchanged rate of protein synthesis. Furthermore the reuse of the amino acid nitrogen provided by protein breakdown was decreased, which may have indicated that amino acids were consumed as metabolic fuel (Table 5).

There are five possible explanations for the observed effects of hypoxia in this investigation. (1) Inefficient energy production: Anaerobic glycolysis, which is the major source of energy at low oxygen tension, is an inefficient means of ATP generation, *i.e.*, net energy gained in a state of complete anoxia is 18 times less effective than that through aerobic oxidation. This postoperative energy deficit appears to be compensated for by accelerating protein breakdown to provide metabolic fuel for the whole body. (2) Prostaglandin release: Hypoxic¹⁴ and ischemic¹⁵ stimulation causes the release of vasodilator prostaglandins (e.g., PGE_2 and PGI_2) from vascular tissue. Increased PGE_2 in the muscle, which ultimately activates lysosomal protease, induces increased muscle proteolysis.^{16,17} (3) Hormonal responses: It has been reported^{18,19} that hypoxic exercise results in marked increases in plasma glucose, lactic acid, free fatty acid, plasma cortisol, and serum growth hormone, and a decrease in serum insulin. The evidence indicates increased fat mobilization and enhanced hepatic gluconeogenesis. (4) Increased amino acid catabolism: There have been some reports of increases in

TABLE 3. ^{15}N Enrichment in Total Urinary N During Continuous Infusion With ^{15}N -glycine, with Calculated Rate of Whole-body Protein Turnover, Protein Synthesis, and Protein Breakdown

Group	Subject No.	Weight g	Infused ^{15}N *	Urinary ^{15}N at Plateau†	Time at Plateau (hours)	Whole-body Protein		
						Turnover‡	Synthesis‡	Breakdown‡
Hyperoxic	1	174.0	0.632	1.952	23.7	446.6	325.9	320.0
	2	173.0	0.516	1.944	26.0	368.2	305.3	223.0
	3	174.0	0.493	1.899	27.7	358.1	287.3	217.9
	4	209.0	0.474	1.692	27.6	321.7	252.1	206.9
	5	207.0	0.496	1.501	22.8	383.1	304.9	266.3
	6	199.0	0.493	1.561	25.5	380.9	301.7	261.1
	7	194.5	0.457	1.637	27.6	344.5	272.0	224.6
	8	199.0	0.465	1.518	27.5	369.4	312.6	246.5
Hypoxic	1	188.0	0.647	2.055	24.0	401.9	263.4	270.4
	2	190.0	0.640	2.324	24.1	347.9	251.4	218.7
	3	194.0	0.625	2.060	25.2	375.3	280.5	248.5
	4	198.0	0.612	1.844	23.9	402.3	313.7	280.6
	5	196.0	0.527	2.001	23.0	322.5	251.0	216.8
	6	188.0	0.600	1.911	24.5	400.8	291.4	257.6
	7	204.0	0.506	1.709	25.9	348.3	202.4	226.6
	8	198.0	0.490	1.959	29.1	303.2	199.3	178.9
	9	212.0	0.452	1.645	29.1	311.1	198.3	198.9
	10	210.0	0.459	1.833	29.0	286.2	164.3	169.7
Control	1	202.0	0.521	1.934	29.4	320.1	270.4	199.3
	2	192.0	0.488	2.275	29.2	268.1	198.3	148.1
	3	198.0	0.484	1.600	29.1	366.7	263.0	245.7
	4	192.0	0.520	2.125	26.3	305.9	253.3	177.7
	5	205.0	0.501	2.202	30.1	266.4	215.5	147.1
	6	212.0	0.468	2.075	32.0	255.3	180.2	133.4

* mgN/hour.

† Atom percentage excess.

‡ mgN/100g/day.

several parameters of amino acid catabolism under hypoxic conditions, e.g., increased hepatic transaminase and urea cycle enzyme activities.^{11,20} (5) Hypoxic proteinuria: Rennie et al.^{21,22} observed this effect not only in native Pruvian Indians dwelling at high altitudes but also in subjects visiting high altitudes, regardless of whether the subjects had been acclimated. Any of these explanations could account for the negative effects of hypoxia.

The use of hyperbaric oxygen therapy in post-traumatic circulatory insufficiency has been established and shown to be effective in cases of chronic circulatory insufficiency, postburn ulcers, and ischemic edema.^{23,24} There is little information, however, on the effect of hyperoxia on protein metabolism, especially in terms of dynamic studies

of protein metabolism under normobaric hyperoxia. In addition to a positive cumulative nitrogen balance, increases were seen in both weight and in the rates of body protein synthesis and breakdown. The rate of protein synthesis was found to exceed that of breakdown and this resulted in a definite improvement in the nitrogen balance. Most of the amino acid nitrogen produced by increased protein breakdown ultimately may have been reused more efficiently to synthesize protein with less of that nitrogen being found in metabolic fuels and excreted in urine (Table 5). Under hyperoxic condition, ATP is generated efficiently, thereby making it more readily available for protein synthesis and fat deposition. This could be another explanation for how cellular metabolic processes, such as

TABLE 4. Summary of Calculated Results for Whole-body Protein Turnover, Synthesis, Breakdown, and Values for Total Urinary and Infused N

Group	Weight (g)	Whole-body Protein			Infused†	Total Urinary†
		Turnover*	Synthesis*	Breakdown*		
Hyperoxic (8)‡	191.2 ± 15.2	371.6 ± 36.4§	295.2 ± 23.7	245.8 ± 36.7§	5.24 ± 0.46	3.18 ± 0.81
Hypoxic (10)	197.8 ± 8.6	349.9 ± 43.7	241.6 ± 48.4	226.6 ± 37.6	5.14 ± 0.44	4.52 ± 0.94§
Control (6)	200.2 ± 7.8	297.1 ± 42.4	230.1 ± 37.3	175.2 ± 42.0	5.08 ± 0.13	2.79 ± 0.87

All values are mean ± SD.

* mgN/100g/day.

† mgN/100g/hour.

‡ The numbers in parentheses are the numbers of rats used.

§ Significant difference from the control group ($p < 0.01$).|| Significant difference from the control group ($p < 0.05$).

TABLE 5. Percentage of N Entering the Metabolic Pool that Is Synthesized into Protein and the Percentage that Is Derived from the Catabolism of Protein

Group	Subject	S/Q · 100*	B/Q · 100†
Hyperoxic	1	73.0	71.6
	2	82.9	60.6
	3	80.2	60.9
	4	78.4	64.3
	5	79.6	69.5
	6	79.2	68.6
	7	78.9	65.2
	8	84.6	66.7
	$\bar{x} \pm SD$	79.6 ± 3.4	$65.9 \pm 4.0\ddagger$
Hypoxic	1	65.5	67.3
	2	72.3	62.9
	3	74.7	66.2
	4	78.0	69.8
	5	77.8	67.2
	6	72.7	64.3
	7	58.1	65.1
	8	65.7	59.0
	9	63.7	63.9
	10	57.4	59.3
	$\bar{x} \pm SD$	$68.6 \pm 7.6§$	$64.5 \pm 3.4§$
Control	1	84.5	62.3
	2	74.0	55.2
	3	71.7	67.0
	4	82.8	58.1
	5	80.9	55.2
	6	70.6	52.2
	$\bar{x} \pm SD$	77.4 ± 6.0	58.3 ± 5.4

Measurements were made at equal levels of protein intake.

* Percentage of n entering the metabolic pool that is synthesized into protein.

† Percentage that is derived from the catabolism of protein.

‡ Significant difference from the control group ($p < 0.01$).

§ Significant difference from the control group ($p < 0.05$).

the formation of protein peptide chains from incorporated amino acids, is directly accelerated by an adequate supply of oxygen.

Although we investigated protein metabolism after surgery by inducing hypoxia (hypoxic hypoxia) and hyperoxia (hyperoxic hyperoxia) through the regulation of the systemic oxygen content and have shown that oxygen has a beneficial effect of oxygen on protein metabolism in early postoperative days, the most important factor for cellular metabolic activities is considered to be local tissue oxygen pressure. There is, therefore, a need for further investigations of not only the most effective F_{iO_2} in terms of improving protein metabolism after surgery but also the relationship between F_{iO_2} and tissue oxygen pressure.

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Who Killed General Surgery?

JOHN A. MANNICK, M.D.

FOR THE PAST decade we have heard repeated public assertions at the meetings of national and regional surgical organizations that general surgery is in dire straits, with its various components being split apart and taken over by surgical specialists or specialists from other disciplines. It seems inarguable that many general surgeons no longer set fractures, operate on head and neck cancer, or even perform arterial reconstructions. It has been a long time since most general surgeons operated on the lung and even longer since Harvey Cushing warned 'Don't let neurological surgery get too far away from general surgery.'¹ Anyone who is not yet convinced that the fragmentation of general surgery is now a major issue for American surgery need only read the thoughtful and challenging address delivered by President Jurkiewicz² to the American College of Surgeons barely 6 months ago.

Because so much has recently been said on the subject, you may rightly ask why I have chosen to address this issue today. There are at least three reasons. First, it is an issue that should be of concern to all of us because the future of general surgery is clearly of critical importance to the future of all of surgery. Second, as a director of the American Board of Surgery at the time the first certificates of special qualifications were approved, I had the opportunity to hear firsthand the discussion and debate that preceded this action, and therefore have some personal knowledge of the history of this controversial move. And third, while I have been a program director responsible for a general surgical residency for 17 years, I have also held one of the certificates of special qualifications from the American Board of Surgery for the past 7 years and thus have had ample time to reflect on the question of subcertification in general surgery from these two disparate vantage points. Whether this exercise has led to wisdom or schizophrenia, I leave to you to decide.

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If the scope of general surgery has been eroded, and there is good evidence that it has, where did all this begin and who is responsible? One group of culprits identified in most discussions of this subject are the surgical specialists. I was unaware of or had forgotten much of the early history of surgical specialization in the United States and, in case some of you are in the same boat, I thought it might be worthwhile to review this process briefly. It is interesting that even at the time the American Board of Surgery was founded in 1937, already there were duly accredited specialty boards in orthopedic surgery, urology, and otolaryngology. Then not long after the American Board of Surgery was incorporated, neurosurgery, plastic surgery, and colorectal surgery formed separate boards. With the latter event, even the lower bowel was seemingly removed from general surgery. If general surgery is not the surgery of guts and glands, what is it? It is somewhat reassuring that the availability of specialty certification in colorectal surgery appears to have had little effect on the practice of the average general surgeon, as we shall see in a moment.

The American Board of Surgery (ABS) has recently received considerable criticism as the organization responsible for some of the fragmentation in general surgery, and it is clear from the record that in its early years the Board was ambivalent about specialization within surgery. For example it did not oppose the formation of the Board of Thoracic Surgery first as an affiliate board of the ABS in 1950 and later as a separate board. While there were good reasons for this action, there also have been a few negative results. In many U.S. hospitals, for example, the thoracic esophagus is out of bounds to expert GI surgeons but is sometimes the province of the coronary artery surgeon. It is at least questionable that a surgeon who focuses his clinical practice on coronary artery grafting is better prepared to manage esophageal problems than a surgeon

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who is skillful at operating on disorders of the stomach, to which the esophagus is attached. Is the costal arch a logical barrier between surgical specialties?

However the ABS has in recent decades been much more steadfast in its opposition to further dismemberment of general surgery. Beginning in the mid 1970s, the Board has attempted to define the scope of general surgery. This definition of the primary components of general surgery has been modified repeatedly by the ABS and, in 1990, includes surgery of the alimentary tract, the abdomen and its contents, the breast, skin and soft tissues, the head and neck, the vascular system and the endocrine system, plus surgical oncology, comprehensive management of trauma, and complete care of critically ill patients.

The ABS and the Residency Review Committee for Surgery (RRC) have struggled with the dilemma of preserving the breadth of general surgery while granting appropriate recognition to groups of surgeons who have concentrated on and claimed special expertise in one or another component of general surgery. To attempt to resolve one such dilemma, the ABS voted in 1972 to issue a certificate of special qualifications in pediatric surgery. This was followed in the same year by a request from the two major vascular surgical societies in the United States for a certificate of special qualifications in vascular surgery. This request was based on evidence that the quality of vascular surgery in the United States tended to be low when the vascular surgical volume of the individual surgeon was low and that the operative experience of the average surgical resident in major arterial surgery was limited.³ The societies proposed further training in vascular surgery after general surgical residency for those who, in the future, would be examined for vascular certification. This request for a vascular certificate sparked a great deal of debate and many negative comments from senior figures in American surgery who were concerned about the possible destruction of what was left of general surgery if such a certificate were issued. On the other side were arguments that the quality of patient care was at stake and that issuing a vascular certificate would ensure control of the ABS, representing general surgery, over vascular surgery and vascular training. The latter arguments at the time were not persuasive and the request for a certificate was tabled by the ABS. However, as organizations characteristically do when faced with an unresolved problem, the ABS voted to form a Committee on Vascular Surgery in 1974 and invited senior representatives from the two major vascular societies to join the committee.

Because certification seemed to be a dead issue, temporarily at least, the committee devoted itself to considering training in vascular surgery and defining standards for adequate training in this component of general surgery. These standards for training in vascular surgery were taken back by the vascular representatives on the ABS to the

joint council of the vascular societies and were ratified by the societies as standards by which to judge the adequacy of vascular fellowship programs.

With what seemed the tacit approval of the ABS, the vascular societies formed their own committee to inspect and certify fellowship training programs in vascular surgery, thus acting as a *de facto* residency review committee for vascular surgery outside the framework of the Accreditation Council for Graduate Medical Education (ACGME), the parent body for all duly constituted residency review committees. This did not appear to be an optimal solution to the problem of vascular training. However under the ACGME, residency review committees inspect and accredit training programs only if there is a board certificate available to graduates of such programs.

As I recall it was consideration of this state of affairs in 1977 that led the ABS to reverse itself on the issue of vascular certification specifically and on the question of further certificates of special qualifications in general. The idea of vascular certification was presented to the Regents of the American College of Surgeons, who, in fact, had no official control over the matter. Nevertheless the American College of Surgeons is one of the original parent organizations with strong representation on the American Board of Surgery and it was clearly appropriate to solicit the Regents' opinion on this new proposal. The Regents first approved the idea of vascular certification and the stumbling block to issuing a vascular certificate became the American Board of Medical Specialties (ABMS), which, as most of you know, is the 'Board of Boards' in which representatives of all specialty boards meet to approve changes in certification proposed by any member board. In the ABMS neurosurgeons, urologists, and cardiothoracic surgeons opposed the vascular certificate probably because the first two groups wanted to do vascular surgery in their areas of interest and a number of cardiothoracic surgeons regularly performed all the vascular surgery in their hospitals and clinics.

Finally in 1980 the American Board of Thoracic Surgery, the American Board of Surgery and the two vascular societies agreed that certificates of special qualifications in vascular surgery could be issued to graduates of cardiothoracic training programs under certain circumstances as well as to residents or fellows completing extra vascular training in general surgical departments, provided that the training guidelines previously set forth by the ABS were met. The title of the certificate was changed to 'special qualifications in general vascular surgery' to mollify the neurosurgeons and urologists, and the proposal was taken back to the ABMS by the ABS in 1981. Meanwhile the regents of the College reconsidered the idea of vascular certification and this time voted against it. However the vote came too late and the ABMS approved the

certificate of special qualifications in general vascular surgery as proposed by the ABS. The stage was then set for the RRC to accredit training programs in vascular surgery.

It is hardly surprising that the vascular certificate that was launched amid controversy has been dogged by controversy ever since. While the issuing of a certificate of special qualifications in pediatric surgery had caused almost no furor because such certification did not interfere with the practice of most general surgeons, the issuing of a vascular certificate by the ABS produced an entirely different reaction. It appeared that the ABS had acted in direct opposition to the regents of the College, who were clearly not pleased with this development. The American Surgical Association put itself on record as opposing certificates of special qualifications because of their perceived negative impact on the status of general surgery. The issue was again debated at length by the ABS, but motions to scrap special certification were voted down. However the names of the vascular and subsequent certificates were changed to 'certificates of added qualifications' rather than 'special qualifications,' thus more clearly indicating that the areas in which the certificates were issued were considered to be components of general surgery.

Despite the controversy caused by the issuing of the vascular certificate, two more certificates of added qualifications have been approved by the ABS, one in surgical critical care in 1984 and one in hand surgery in 1986. One impetus for issuing these certificates was perhaps the recognition that other boards were already, or were planning, issuing such certificates and it was thought that general surgeons would be forced out of these areas if no equivalent certificate were available to them. Certificates of added qualifications in other areas of general surgery, such as surgical oncology and head and neck surgery, have been considered by the ABS but have not been approved. In fact in its January 1990 meeting, the ABS voted a moratorium on further certificates of added qualifications, a course of action urged by the Council of the American Surgical Association and the Advisory Council for Surgery of the American College of Surgeons.

In issuing its certificates of added qualifications in areas defined as lying within general surgery, has the ABS been the villain in dismembering general surgery, or has the ABS acted with foresight to preserve the scope of general surgery? One problem in discussing this issue is a tendency by many individuals to confuse surgical training and surgical practice. Practice patterns in general surgery vary widely across the United States and there are probably a few general surgeons in small cities and towns who regularly work in all or nearly all of the areas defined by the ABS as primary components of general surgery. However this clearly has not been the norm in most cities for many years and certainly has not been the experience of the average general surgeon in the United States. Recent

practice experience of general surgeons applying to the ABS for recertification bears this out. Perusal of the data in Table 1 indicates that the average general surgeon in the 1987 recertification group did very little thoracic (median, 1 case), pediatric (median, 2 cases), arterial (median, 0 cases), or head and neck cancer surgery (median, 0 cases) in the preceding 2-year period. A comparison of the 1-year operative experience of the 1980 and 1987 recertification groups (Table 2) shows that if any effect of vascular certification is seen it is paradoxically a slight increase in arterial surgery for the 1987 group, although, as we have just seen, the median number of such cases remained zero. It is heartening that most surgeons who limit their practices chiefly to vascular or pediatric surgery continue to take and pass the recertification examination in general surgery, even though their practices include few of the cases most frequently performed by general surgeons.

Table 3 shows the procedures most frequently performed by general surgeons in 1985 and indicates that surgery of the breast, bowel, and biliary tract dominate along with herniorrhaphy. As we have seen in Table 1, much of the bowel surgery is colon and rectal surgery and this is 36 years after the establishment of a separate board of colorectal surgery. The practice of most general surgeons does not appear to have been affected very much by the availability of special certification in this area.

From the data we have just reviewed, it is apparent that the average general surgeon seldom encounters cases in several of the components of general surgery as defined by the ABS. In fact how many general surgeons in this organization, many of them the leaders of our profession, have or even desire to have a practice that regularly includes Whipple operations, kidney transplants, femoro-tibial vein grafts, care of major burns, ileoanal pull-through procedures, resection of oropharyngeal cancer, bile duct reconstructions, and repair of complex hand injuries? Probably not many. However I hope that surgical residents in the training programs directed by many members of this organization would perform all of these procedures before they graduate.

Is it foolish to continue to recommend the broadest possible experience in general surgical training when, after completion of the training, most general surgeons will have a practice of much narrower scope? I am convinced it is not. An individual who has completed the broadly based general surgical residency currently mandated by the ABS is, I believe, much better equipped to practice skillfully in whatever area or areas of general surgery he or she elects to focus on. For example I would not want my colon cancer removed by a surgeon who had not had a sizable experience in dissecting out blood vessels and managing vascular injuries. Conversely I would not want my aortic aneurysm repaired by a surgeon who had not had plenty of training in surgery of the bowel, stomach,

TABLE 1. Summary of Operative Experience: 1987 to 1988 Recertification Examination Sample-ABS

Operation	Mean	Median	Range	Percentage with One or More Cases
Abdominoperineal resection	2.2	1	0-23	60
Adrenalectomy	0.3	0	0-10	18
Appendectomy	25.1	22	0-83	90
Cholecystectomy	43.8	37	0-216	91
Cholecystostomy	0.4	0	0-9	22
Common duct operation	8.0	6	0-47	82
Colectomy	22.5	17	0-175	90
Colostomy	5.5	3	0-46	82
Enterostomy	3.8	2	0-52	59
Exploratory laparotomy	11.7	7	0-175	86
Gastroenterostomy	2.2	1	0-35	52
Gastrectomy	4.9	3	0-33	87
Gastrostomy	6.2	3	0-76	74
Herniorrhaphy, inguinal	45.9	40	0-259	89
Herniorrhaphy, other	16.2	14	0-103	89
Pancreas operations	2.3	1	0-32	57
Small Bowel resection	6.8	4	0-167	79
Splenectomy, disease	1.8	1	0-21	54
Vagotomy	3.1	2	0-60	61
Total GI and abdomen	212.9	197	0-1160	95
Hemorrhoidectomy	9.6	5	0-165	79
Fissures and fistulae	7.1	3	0-99	79
Total anorectal	16.7	10	0-242	86
Radical mastectomy	0.2	0	0-5	10
Modified radical mastectomy	10.9	8	0-70	81
Simple mastectomy	3.1	1	0-52	62
Biopsy	42.6	30	0-270	85
Total breast	56.8	43	0-371	87
Abdominal wall	0.3	0	0-18	8
Central nervous system	0.0	0	0-0	0
Cervical	0.2	0	0-18	6
Gastrointestinal	2.8	0	0-251	27
Hernia	7.5	0	0-147	47
Rectal	0.2	0	0-10	7
Thoracic	1.2	0	0-233	4
Urologic	0.6	0	0-29	8
Total pediatric	12.8	2	0-687	54
Craniotomy	0.0	0	0-1	0
Laminectomy	0.0	0	0-1	0
Glossectomy	0.1	0	0-15	2
Parotidectomy	0.7	0	0-16	25
Radical neck dissection	0.3	0	0-27	9
Resection mandible/maxilla	0.1	0	0-20	2
Thyroid	5.2	3	0-49	75
Parathyroid	1.2	0	0-30	32
Total head and neck	7.6	4	0-117	79
Diaphragmatic hernia	1.1	0	0-28	29
Esophagectomy	0.9	0	0-20	23
Excision mediastinal tumor	0.2	0	0-9	11
Open cardiectomy	6.2	0	0-781	6
Pneumonectomy/lobectomy	2.0	0	0-50	22
Segmental wedge exc lung	1.2	0	0-37	18
Thoracotomy	2.1	0	0-92	29
Thoracoplasty	2.3	0	0-421	11
Closed cardiac	0.7	0	0-70	8
Total thoracic	16.6	1	0-818	57
Brachiocephalic	7.1	0	0-119	33
Thoracic	0.5	0	0-50	8
Abdominal peripheral aneurysm	4.3	0	0-57	44
Abdominal occlusive	3.8	0	0-44	41
Lower extremity occlusive	10.8	0	0-89	49
Portal decompression	0.8	0	0-46	17
Varicose veins	4.0	3	0-24	68
Sympathectomy	0.7	0	0-10	22
Total vascular	32.0	8	0-253	79

TABLE 2. Comparison of Operative Experience (1 Year) of 1980 and 1987 to 1988 Recertification Groups-ABS

Operation	1980 Average	1987 to 1988 Average
Brachiocephalic	1.75	3.55
Thoracic	0.12	0.23
Abdominal peripheral aneurysm	1.31	2.18
Abdominal occlusive	1.39	1.88
Lower extremity occlusive	3.19	5.41
Portal decompression	0.25	0.38
Varicose veins	3.73	2.04
Sympathectomy	0.71	0.36
Total vascular	12.45	16.02

biliary tract, and pancreas. If you agree with me that the broadest possible training is desirable for most, if not all, general surgeons regardless of how focused their practice after residency may become, then it seems obvious that general surgical training should be protected from further encroachment by surgical specialty boards and residency review committees demanding that their residents do increasing numbers of cases in areas previously considered part of general surgery for their specialty residencies to remain accredited. This sort of territorial aggrandizement by expansion of the essentials of approved residency training is familiar to you all. Perhaps the most aggressive practitioners of this kind of annexation are the otolaryngologists, but there are a number of others.

The chief battle ground where these 'turf' wars are fought is the ABMS. General surgical training is defended at the ABMS by representatives from the ABS who have over the years opposed usurpation of general surgery by specialty boards with vigor and with a commendable degree of success. This activity of the ABS is seemingly overlooked by many of its critics. Until the past year the American College of Surgeons declined to adjudicate 'turf' disputes between surgical specialties, and while general surgeons are still the largest single specialty within the College, they are, in fact, a numerical minority of College fellows. Therefore it has been left to the ABS, with the support of the RRC, to defend general surgery from encroachment from all sides.

If the directors of the ABS are the guys with the white hats, defending general surgery from aggressive specialty boards, why have they perversely been the ones to legislate the dismemberment of general surgery by issuing certificates of special or added qualifications, thus apparently eliminating portions of general surgery from the practice of the average diplomate of the ABS? To some of the senior members of the ABS it may seem that while the ABS made statesmanlike and rational decisions when we were active members, it has acted without significant reflection and understanding of the important issues now that we are no longer consulted. I suspect, however, that most of us would concede that not all the brains and fore-

sight in American surgery are possessed by surgeons older than 60 years. Perhaps we might admit that it is possible that the ABS, with its changing membership, adapts to changing circumstances as its collective wisdom deems best.

For example a case can be made for the proposition that by establishing a certificate in vascular surgery, the ABS was simply converting a *de facto* mechanism for approving advanced training in vascular surgery administered by the vascular societies to a *de jure* mechanism administered by generally recognized accrediting bodies. In doing so, the ABS and the RRC at least regained control over training in vascular surgery and were able to ensure that vascular surgical residencies were accredited only in those institutions in which there was a sufficient volume of vascular surgery that each graduating general surgical resident did at least 40 major arterial reconstructions while leaving at least 70 such cases for the vascular resident. This issue had not been high on the agenda of the vascular societies. There is reasonably hard evidence that this policy has resulted in an increase in the vascular surgical experience of general surgical residents in the United States from an average of about 10 to 15 major arterial reconstructions per resident to about 60 such cases today. Contrast this with the situation in thoracic surgery in which general surgery residents have, on the average, little experience with operations on the lung, even though many of them will be required to manage injuries to this organ in their practices. Granted there are more vascular operations than lung resections to be done in most teaching hospitals, but the comparison is probably still valid.

It seems reasonably clear, at least to me, that by continuing to exercise control over training in the components of general surgery for which added certificates are available, the ABS and the RRC have ensured the broadest

TABLE 3. Selected Operative Procedures Performed by Board-certified General Surgeons, 1985

Procedures	Percentage of General Surgeons Who Performed the Operation
Cholecystectomy	86.5
Resection of large bowel	85.6
Appendectomy	84.5
Hernia repair (all types)	84.2
Mastectomy	83.1
Resection of small bowel	83.0
Laparotomy (emergency)	80.7
Vagotomy	78.3
Gastrectomy	78.0
Thyroidectomy	75.9
Varicose veins, excision and ligation	65.7

From Karnell LH. The surgical manpower survey: selected operative procedures performed by board-certified general surgeons. ACS Bulletin 1987; 72:9-13.

possible training for all general surgery residents. It can be argued that this would have been simpler if no additional certificates had been granted. However I am convinced that the drive for recognition for extra training in pediatric and vascular surgery within or without the ABMS was nearly irresistible and if certification in those areas outside the ABS now existed, the excision of those components from general surgical training programs already would be complete.

What about the effect of certificates of added qualifications on the practice of general surgery? The ABS has consistently maintained that it intended no relationship between added certification and privileges to practice the component of general surgery covered by the certificate. This assertion by the ABS clearly has not been reflected in surgical practice. It surprised and disturbed few general surgeons that complex pediatric surgery was done by certified pediatric surgeons because most general surgeons had not performed such operations in any case. However many thoughtful general surgeons are disturbed by the evidence that vascular surgery in the United States is increasingly performed by surgeons with vascular certificates. According to the latest estimates supplied by Dr. Calvin Ernst,⁴ the current President of the Society for Vascular Surgery, about 70% of major arterial surgery in the United States is now being performed by members of the major vascular societies, many of whom hold certificates in vascular surgery from the ABS.

Is this a bad thing for the country and a bad thing for surgery? What little evidence is available suggests that patient outcome is more related to the experience of the operating surgeon in some areas of surgery than in others, and major arterial surgery is one of the areas in which this relationship appears to exist.⁵ But are there not many instances in which younger surgeons with certificates are supplanting senior, better qualified surgeons trained before vascular residencies and certificates were available? As one of those senior surgeons, I can testify to the fact that during a 6-year period, the ABS offered the opportunity to take the vascular certifying examination to ABS-certified surgeons who could demonstrate significant contributions to and current operative experience in vascular surgery. Perhaps the standards were set too high, but they were applied evenhandedly and there were no grandfathers who received certification without taking the examination. There may be good general surgeons experienced in vascular surgery who were excluded by this process, but their number is probably not large.

Does not the vascular certificate limit the scope of the surgical practice available to the young general surgeon completing his or her residency? This undoubtedly depends on the size of the community and the size of the hospital in which he or she chooses to practice. It seems

clear that in larger cities and in larger hospitals, vascular surgical privileges are increasingly restricted to those surgeons with vascular certificates or at least to those with current significant experience in this area. However this is apparently not and may never be true in many smaller communities, although the threat of litigation may increasingly drive both surgeons and hospital boards to seek the perceived protection afforded by the vascular certificate. It is also likely that the increased malpractice premiums required to practice vascular surgery, as well as quality of care and other issues, were gradually concentrating vascular cases in the hands of the surgeons with sizable experience in this area in many states before the issuing of vascular certificates. This idea is supported by the operative experience reported by candidates for general surgical recertification a decade ago (Table 2).

The impact of the certificates in critical care and in hand surgery on general surgical practice is difficult to determine. However I am convinced that if the certificate in critical care had not been approved by the ABS, we would soon have no surgeons in charge of intensive care units in major United States hospitals because their counterparts in anesthesiology and internal medicine would hold certificates in critical care medicine from their respective specialty boards and could, in time, persuade hospital administrations that certified competence in this area was essential for every intensive care unit director if the institution were not to run the risk of liability for inadequate supervision of its intensive care units.

Has the issuing of certificates of added qualifications by the ABS then contributed to the erosion of the scope of general surgery? It seems to me the ABS has approved these certificates only when it had no practical alternative and in so doing it has at least maintained control over training in those areas and has assured general surgical residents experience in these components of general surgery by insisting on such training in its requirements for eligibility to take the ABS examination. I believe the ABS and the RRC, both of which have received criticism in the past 8 years, deserve the thanks and support of those of us who are sincerely interested in preserving the broadest possible general surgical training in our residencies. I am convinced the ABS and RRC are trying to maintain a truly general surgical residency against the opposition of articulate and determined representatives of various specialties within and outside of surgery. It is time to stop Board bashing and offer the ABS and the RRC our help and support, in addition to our advice. In this regard I am heartened by the recent decision of the officers of the American College of Surgeons to set up a mechanism for discussion and perhaps resolution of conflicts between surgical specialties. Would it not be wonderful if all surgical specialists could approach the ABMS and the

ACGME united rather than at odds? At the very least, think of the increased clout our profession would have in these important arenas.

To return to the title of this talk, 'Who Killed General Surgery?' perhaps the answer is that we all did if we are talking about abandonment of a surgical practice that encompasses all components of general surgery, as defined by the ABS. The focus of many of us here on one or another aspect of general surgery in our clinical and research endeavors is, in part, why we are members of the American Surgical Association today. And as we have seen, we are not just anomalies produced by academia but are, more than we might suppose, representative of general surgeons throughout North America. If, however, we are talking about a broadly based 5-year general surgical residency with graded responsibility and rich in operative experience, then we can answer the question 'who

killed general surgery?' with the assertion that general surgical training is still alive and well in the United States. With our help, I believe our representatives on the ABS and the RRC have a reasonable chance of keeping it that way.

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A Personal Experience with 100 Consecutive Total Colectomies and Straight Ileoanal Endorectal Pull-throughs for Benign Disease of the Colon and Rectum in Children and Adults

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In 1974 total colectomy and ileoanal straight endorectal pull-through (ERPT) were first used at our institution for the definitive management of total colonic Hirschsprung's disease in infants and children. Early success with this operation encouraged us to use this procedure in children and adults with ulcerative colitis and familial polyposis in 1977. Since 1974 we have performed total colectomy and straight ileoanal ERPT on 100 consecutive patients with ulcerative colitis (79), familial polyposis (19), and total colonic Hirschsprung's disease (10). Patients who have undergone a colectomy and ERPT but have not had their temporary ileostomy closed have been excluded from this report. This group of patients represents the only large series of straight ERPTs available for comparison with the various reservoir modifications that have been reported. All operations were performed under the direction of the author. The mean age at surgery was 20.6 ± 9.8 years, with a range of 1 to 48 years. Forty-six patients were younger than 18 years at the time of operation. All patients with ulcerative colitis and familial polyposis underwent a temporary loop ileostomy with total abdominal colectomy with ERPT; the 10 infants and children with Hirschsprung's disease underwent the total colectomy and ERPT without a back-up ileostomy. There were two deaths in this series, one from fulminate hepatic failure in the late postoperative period and the other from multiple bowel fistulas and sepsis in a teenager with Crohn's disease, in whom the initial diagnosis was ulcerative colitis. Follow-up has ranged from 3 months to 15 years. There were 13 cases of adhesive bowel obstruction, seven of which required an enterolysis. Pelvic sepsis occurred in three patients, two of whom required operative drainage. Two women developed rectovaginal fistulas, which healed with temporary diversion. Minor wound infections occurred in five patients. There were no anastomotic leaks, nor were any cases of pouchitis encountered. In five patients permanent conversion to a Brooke ileostomy was required.

Mean stool frequency 3 years after surgery was 7.7 per 24 hours. Daytime continence was achieved in all patients. Occasional nocturnal soiling occurred in 11.1% of patients at 1 year and was absent by 3 years. Neither age nor diagnosis (ulcerative colitis *versus* familial polyposis) affected stool frequency. The straight endorectal ileoanal pull-through compares favorably with pull-throughs using various reservoir procedures (7.7 *versus* 7 stools per 24 hours) and appears to have a lower incidence of major complications (0% pouchitis *versus* 14% to 26%, 0% daytime incontinence *versus* 6%, and 3% pelvic sepsis *versus* 5% to 7%). Therefore the straight ERPT remains an appropriate alternative for both children and adults with benign disease of the colon and rectum.

MARTIN'S LANDMARK REPORT in 1977 ushered in a new era in the management of ulcerative colitis.¹ Most centers initially used the straight pull-through method for patients with ulcerative colitis and familial polyposis. However disenchantment with high stool frequencies and a significant incidence of complications prompted these various groups to develop a variety of reservoirs to increase rectal capacitance and, thereby, decrease stool frequency.²⁻¹⁰ In essence a Kock-type pouch was added to the pull-through.¹¹ The theoretical and physiologic advantages of a reservoir have been recently reviewed by Wong et al.¹² With the introduction of the reservoirs, however, has come a number of complications not seen with the straight endorectal pull-through (ERPT), such as pouchitis and a higher incidence of pelvic sepsis.¹³⁻²²

Our experience with the straight ERPT at the University of Michigan Medical Center has been quite different than

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the experience reported by other centers, with a stool frequency comparable to that seen with reservoirs and an incidence of complications lower than that reported with the various pouches.²³⁻³⁰ Because this group of patients represents the only large series of straight ERPTs in children and adults, we have reviewed our experience with this procedure so that our results can be compared with the many series using different types of reservoirs.

Materials and Methods

Between July 1977 and October 1989, 100 children and adults (71 with ulcerative colitis, 19 with familial polyposis, and 10 with total colonic Hirschsprung's disease) underwent total colectomy and straight ileoanal ERPT under the direction of the author. Patients who had not yet undergone closure of their temporary loop ileostomy were excluded from this review. The mean age at operation was 20.6 ± 9.8 years (range, 1 to 48 years). The mean age of the children with Hirschsprung's disease at the time of operation was 17 months and the mean age of the children and adults with ulcerative colitis and familial polyposis was 22.8 ± 10.0 years at the time of surgery. There were 58 female and 42 male patients.

In all patients the diagnosis was confirmed histologically after sigmoidoscopic or colonoscopic examination. In the children with Hirschsprung's disease, the diagnosis was made with a suction rectal biopsy.³¹

The operative technique has been described in detail in previous reports.²³⁻²⁵ The mucosal proctectomy is entirely carried out from the abdominal approach, with removal of an intact mucosal and submucosal tube. A 4- to 5-cm rectal muscular cuff is left and the ileoanal anastomosis is performed 1 cm above the dentate line. The anastomosis is performed with absorbable polyglycolic acid sutures and the muscular cuff is drained with a sump suction catheter for 24 to 48 hours after operation. The top of the rectal cuff is tacked to the pull-through ileum with silk sutures. Before closure of the abdomen, a temporary loop ileostomy is created in the right lower quadrant of all patients with ulcerative colitis and familial polyposis. None of the children with Hirschsprung's disease underwent a diverting ileostomy. The ileostomy was closed 2 to 3 months after the ERPT.

Follow-up was complete in this group of 100 patients and involved monthly visits for the first 6 months, visits every 3 months for the remaining 6 months, and then yearly visits. Sigmoidoscopy was carried out on all patients with ulcerative colitis yearly and every 6 months in patients with familial polyposis; biopsies were taken to detect dysplastic changes in patients with ulcerative colitis and any evidence of new polyp formation or malignant degeneration in the cases of familial polyposis.

Stool frequencies were compared at various time intervals and between age groups and diagnosis using the paired Student's *t* test.

Results

The follow-up has ranged from 3 months to 15 years. There have been two deaths in the series (operative mortality rate, 2%). The first occurred in a teenager with ulcerative colitis and pericholangiolitic hepatitis who developed fulminate hepatic failure 8 months after surgery. The second was in a 13-year-old girl who had an initial diagnosis of ulcerative colitis and underwent a colectomy and an ERPT. After closure of her loop ileostomy, she developed severe diarrhea and intestinal obstruction requiring multiple operations. Eventually she developed multiple enterocutaneous fistulas and invasive sepsis and died 2.5 years after her ERPT. Histologic evaluation of her small intestine at autopsy revealed extensive Crohn's disease. Thirteen patients developed adhesive intestinal obstruction, seven of whom required an enterolysis. Two patients developed pelvic abscesses, which required operative drainage, and a third patient developed a pelvic phlegmon that resolved with intravenous antibiotics. Rectovaginal fistulas developed in two women and both healed with temporary intestinal diversion. There were five minor wound infections.

In six patients mild narrowing of the ileoanal anastomosis was found and this responded easily to early digital rectal dilatation. There were no anastomotic leaks encountered at the ileoanal anastomosis. No patients developed clinical or histologic evidence of pouchitis during the entire follow-up period.

Five patients (5%) were converted to a Brooke ileostomy. One additional patient with familial polyposis was found to have an anaplastic carcinoma at the anal margin of the mucosal proctectomy specimen on histologic examination and required abdominal perineal resection 1 week after the ERPT. One of the five patients, a 10-year-old girl, developed recurrent symptoms of inflammatory

TABLE 1. Postoperative Complications in 100 Patients Undergoing Total Colectomy and Ileoanal Endorectal Pull-through

Complication	Percentage of Patients with Complication
Adhesive intestinal obstruction	13
Adhesive intestinal obstruction requiring enterolysis	7
Pelvic abscess	2
Rectovaginal fistula	2
Conversion to ileostomy	5
Minor wound infection	5

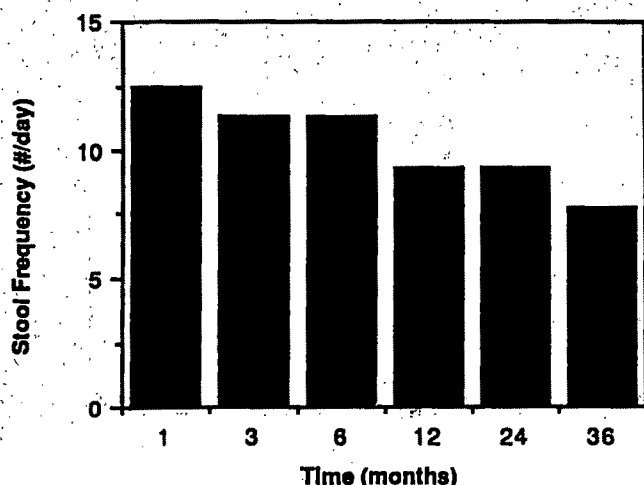


FIG. 1. The stool frequency for the entire series decreased during the 3-year period to a value of 7.7 ± 4.3 per 24 hours.

bowel disease after her ERPT and colectomy. The histologic diagnosis of the colon and terminal ileum specimens was ulcerative colitis. A repeat biopsy of her small intestine revealed Crohn's disease and she was converted to an end ileostomy. A second patient underwent a sigmoidoscopy at another institution shortly after closure of his ileostomy, at which time the pull-through ileum was separated from the rectal cuff. He developed a huge rectoperineal fistula that was treated with a end ileostomy. It is hoped that this ileostomy will be able to be closed in the future. Only three patients (3%) were converted to an ileostomy because of dissatisfaction with their stool frequency (between 10 and 15 per 24 hours). All three patients were continent during the day and at night.

Daytime continence was achieved in all but two patients within 3 months after ileostomy closure, and reached 100% 1 year after operation. Seven patients (7%) experienced minimal nighttime soiling during the first year after ileostomy closure; this nocturnal leakage disappeared 2 years after surgery.

Stool frequency progressively declined after operation, reaching a value of 7.7 ± 4.3 per 24 hours 3 years after the pull-through (Fig. 1). All patients were able to evacuate spontaneously immediately after ileostomy closure. Stool frequency was also analyzed by age groups and diagnosis. There were no statistically significant differences between those patients younger than and older than 18 years (6.3 ± 4.1 versus 9.0 ± 4.2 ; Fig. 2). Likewise patients with familial polyposis had the same stool frequency 3 years after operation as those with ulcerative colitis (7.8 ± 2.4 versus 9.0 ± 4.5 , Fig. 3). In addition age did not appear to be a factor in stool frequency when analyzing the ulcerative colitis and familial polyposis patients separately (Figs. 4 and 5). The children with total colonic Hirschsprung's disease experienced 3.5 stools per 24 hours 3 years after the ERPT.

Discussion

A review of the world literature in 1985 revealed that more than 500 ERPTs had been performed for ulcerative colitis and polyposis, the large majority of which involved a reservoir.²⁵ Because no institution has done enough straight ERPTs to adequately evaluate and compare with their reservoir procedure, and because almost all the straight ERPTs were done during each center's early experience with the entire procedure, when the learning

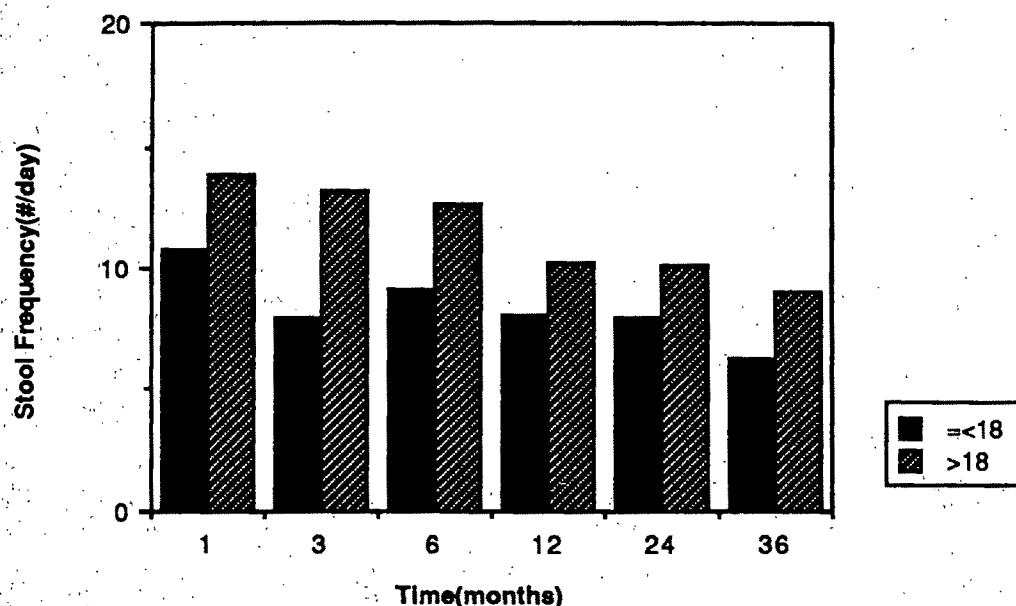
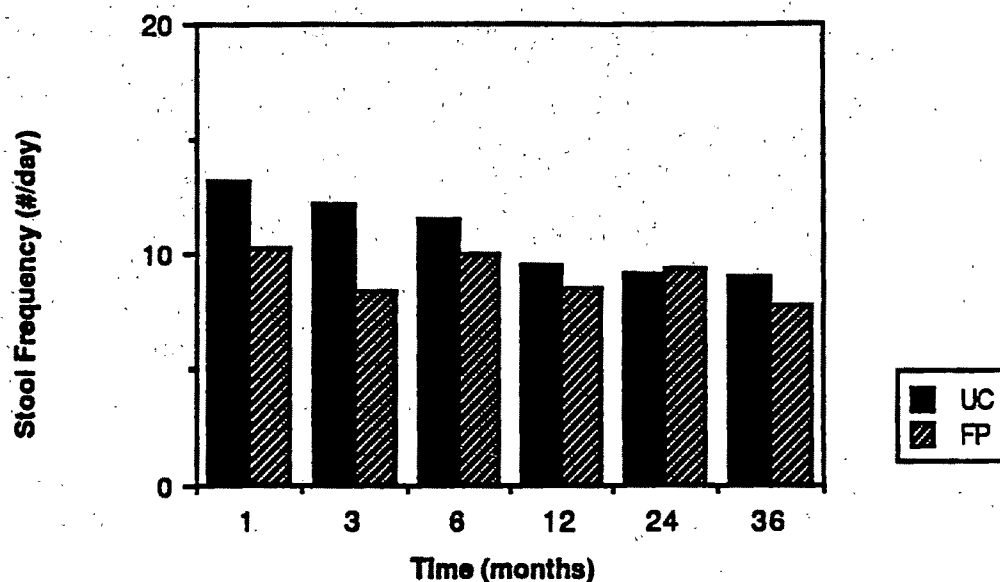


FIG. 2. A comparison of stool frequency in patients less than and more than 18 years of age for the entire series shows that there was no significant difference at 3 years (6.3 ± 4.1 vs. 9.0 ± 4.2).

FIG. 3. There was no significant difference in stool frequency between patients with ulcerative colitis (UC) and familial polyposis (FP) (9 ± 4.5 vs. 7.8 ± 2.4).



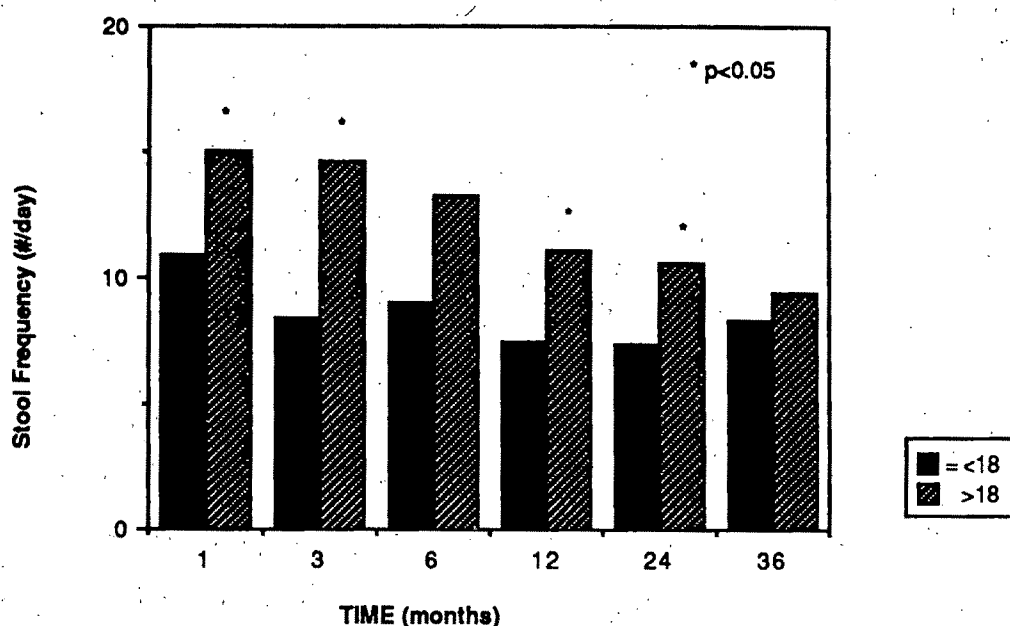
curve was steep, it is impossible to equitably compare the two procedures. The stool frequencies reported with the various reservoirs have ranged from 4 to 9 per day (5 to 7 for the J-pouch,^{13,14,18,20-22} 4 to 9 for the S-pouch,^{16-18,21,23} and 6 for the lateral ileal reservoir¹⁵). Recently we tried to evaluate the various reservoir procedures with the straight ERPT in an experimental model and found that there were no differences in any of the clinical and physiologic parameters studied between the various reservoir procedures and the straight ERPT.³²

The incidence of pelvic sepsis in the various series of reservoirs reported ranges from 3% to 20%.^{8,9,13,15,17,18}

^{20,21,33} This high incidence is not surprising in view of the long suture line that must be placed within the rectal cuff with the various reservoir procedures. In the current series, pelvic abscess occurred in two patients (2%), both of whom required operative drainage; and a pelvic phlegmon, responsive to antibiotic therapy, occurred in a third patient.

Clearly the most serious complication of the reservoirs is pouchitis. The incidence of this complication varies from 5% to 25%.^{10,13,15,17,18,20,21,33} This is one complication that can be completely avoided with the straight ERPT; none of our patients developed any evidence of pouchitis. Nicholls found that 90% of the reservoirs that were sub-

FIG. 4. Age appeared to have no effect on the stool frequency among the ulcerative colitis patients.



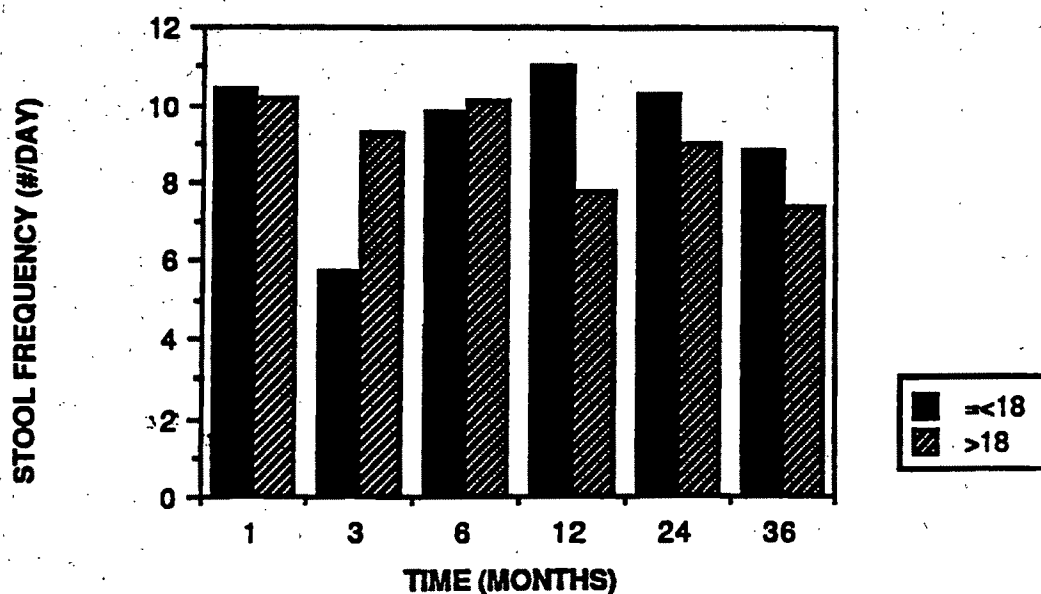


FIG. 5. Age appeared to have no effect on stool frequency among the familial polyposis patients.

jected to biopsy showed evidence of chronic and acute inflammation.^{10,18} All of our patients have undergone an annual or semiannual biopsy of their pull-through ileum; none of these biopsies have shown any significant inflammation.

Adhesive intestinal obstruction is a significant complication in all the series reported, including our own. The incidence ranges from 8% to 35%, with a significant number of these patients requiring an enterolysis.^{8-10,12,13,15,17,20-22}

Spontaneous evacuation has been noted to be a problem for patients who have undergone the S reservoir. One series reported a 53% incidence of inability to spontaneously evacuate, and another more recent series reported an 11% incidence of this.^{17,33}

Although blood was commonly used for the first 50 patients in this series, only 10 of the last 50 patients received transfusions during the operative procedure. In all cases except one, only one unit of blood was administered.

Finally the sole purpose of a reservoir is to increase rectal capacity and thereby decrease stool frequency. We have shown recently that the neorectum created by the straight ERPT progressively dilates during the first 2 years after operation and develops a normal appearance on barium enema (suggesting normal rectal capacity) between 1 and 2 years after surgery.³⁰ This is consistent with the clinical observation that initially the stool frequencies on the average are somewhat higher with the straight ERPT than with the reservoir modification; however these differences tend to disappear 1 to 2 years after the procedure.

The data from this series of patients confirm that the straight ileoanal ERPT is an appropriate alternative procedure (compared to the ERPT with a reservoir) for chil-

dren and adults with ulcerative colitis, familial polyposis, and total colonic Hirschsprung's disease, with comparable functional results and fewer complications than are seen with the reservoir procedures.

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DISCUSSION

DR. KEITH A. KELLY (Rochester, Minnesota): Dr. Coran, I enjoyed your paper and congratulate you on a fine series of 100 consecutive cases of straight ileo-anal anastomosis, that is, an anastomosis made with no ileal pouch. These results are excellent. They are comparable to those of other large series reported recently from around the world. Your patients healed well, they had few complications, good control, and little diarrhea. Only five ended up with a permanent ileostomy.

I have two questions for you. The first is, what about the first 6 months after operation? Did the patients have any problems with troublesome diarrhea or incontinence during this time?

The distal ileum has a small capacity. It only holds about 15 to 30 mL. Dilatation does take place with time. After the first 6 months to 1 year, the patients may then have a satisfactory fecal reservoir. However, at first the distal ileal capacity is small and I would expect your patients to have troublesome diarrhea and some incontinence.

We tried the straight ileo-anal anastomosis in 50 patients at Mayo a few years back, and we did notice that at least in our adult patients, diarrhea and incontinence were present during the first 6 months to 1 year. When we studied these patients in the laboratory, their distal ileal segment was poorly distensible. Moreover, when the segment was distended, the patients had large contractions, which were propulsive and caused leakage. So, Dr. Coran, what about the first 6 months?

The second question relates to ileal 'pouchitis.' I presume what you mean here is that there is no terminal ileitis in the distal ileum anastomosed to the anal canal. You did indicate that you had endoscopic and histologic evidence that that was the case, but you did not show us any of that data.

We found in studying our own patients with the straight pull-through that some of them did have a nonspecific ileitis in the distal ileum. In a few cases with symptomatic distal ileitis, resection of that segment was necessary. Thus, our early data did not allow us to breathe easy about the "pouchitis" question even in the straight ileo-anal patients. Stasis is present in the terminal ileum after ileoanal anastomosis. At least, in the

colitis patients, one might expect in some patients an inflammatory response to this stasis and to the bacterial overgrowth that accompanies it.

DR. HARVEY J. SUGERMAN (Richmond, Virginia): You stated in the abstract that there was no difference in stool frequency when age was used as a criterion. However, in your data of ulcerative colitis and familial polyposis patients, the average number of stools were nine and ten per day. Since the patients with Hirschsprung's disease were excluded from that group, I wonder if there was a statistically significant difference in stool frequency between the Hirschsprung's patients, who had to be very young, and your older patients with ulcerative colitis and familial polyposis, as the average for the entire group was 7.7 stools per day?

DR. ALVIN L. WATNE (Peoria, Illinois): Our group had a small experience in this operation, and Dr. Hrabovsky and I found that the children tolerated the straight ileo-anal pull-through much more readily than the adults. As Dr. Coran implied, the first 6 months is a very difficult adjustment time, and we found that the children tolerated this adaptation time better than the adults. I would appreciate their comments on that division of their patients.

DR. ARNOLD CORAN (Closing discussion): I would like to preface my answers to the specific questions by just stating that the motivation for submitting the paper was that there is a sense around the country, around the world, that the straight endorectal pull-through is inappropriate for adults or even for older children. I wanted to present this data to show that, in fact, it does appear to work reasonably well for both older children and adults.

In response to Dr. Kelly's question, the first 6 months is not as good as the second year. There is no question about it. In general, the stools are around 10 to 12, sometimes to 15, per 24 hours. However, they are continent. It is extremely unusual for them to be incontinent. I don't know whether this relates to the technique that we use for doing the

endorectal dissection or something else, but they are continent. They feel better. The patients with ulcerative colitis are so relieved of their disease by having their colon taken out that, even though that is a fairly significant stool frequency, over-all their lifestyle is much improved and they are happy with the operation. But, in fact, the stool frequency is greater than the number that we see at 2 years or, as I showed in the slide, at 36 months.

The pouchitis question is a legitimate one. We have actually performed biopsies routinely, as I mentioned in my talk, on the ileo-anal anastomosis. There is really no significant ileitis there. Most of the slides come back showing no significant abnormality. Occasionally, very mild inflammation is seen, which is of very little significance histologically and of no significance clinically because none of the patients have had any trouble with pouchitis.

In answer to Dr. Sugerman's question about the Hirschsprung patients, there were ten children with total colonic Hirschsprung's disease. In fact, in that group of ten children, there were four of them who had Hirschsprung's disease extending through the ileum up to the distal jejunum; those patients had their pull-throughs performed just as I described. That

is, they had an ileectomy and colectomy and a jejuno-anal anastomosis. Their average stool frequency is between 3.5 and 5 per 24 hours, a little bit less than the other group, but the number of patients is so small that it didn't have any statistical effect on the stool frequency for the entire group.

In answer to the last question, Dr. Watne's, I think the point I was trying to make was in the stool frequency slides, namely, that age did not make any difference. We analyzed several age groups. I just showed the slide analyzing the groups under and over 18 years of age where there was no difference, but in fact, if you look at the group over and under 30 years of age, a question that may be of more importance to some members of the audience, there were no differences there either. The other interesting finding was that there were no differences, and I didn't expect to find this, between the patients with polyposis and ulcerative colitis. My impression anecdotally was that the familial polyposis patients did better, but, in fact, when we analyzed the numbers, they were the same. That is not consistent with the findings at the Mayo Clinic, where they found the polyposis patients had a lower stool frequency than the ulcerative colitis patients.

The Evolution of Techniques and Indications for Lung Transplantation

JOEL D. COOPER, M.D.

The techniques and indications for lung transplantation have evolved significantly in the past 6 years. We initially restricted single-lung transplantation to patients with pulmonary fibrosis and developed the double-lung transplantation procedure for patients with emphysema or cystic fibrosis. However, with the double-lung procedure, a 25% mortality rate resulted from ischemic complications at the tracheal anastomosis. The technique was altered to incorporate bilateral bronchial anastomosis, with a resulting reduction in airway complications. The double-lung transplantation procedure continued to have significant drawbacks, including intraoperative and postoperative hemorrhage, and cardiac complications due to prolonged cardiopulmonary bypass, ischemic cardiac arrest, and extensive manipulation of the heart. These problems recently have been addressed with a much simplified procedure incorporating a bilateral transverse thoracosternotomy, replacement of the right lung without cardiopulmonary bypass, and replacement of the left lung with or without a short period of partial bypass. This procedure has been successfully used for emphysema and for cystic fibrosis. The technique of single-lung transplantation also has been simplified and indications have been expanded to include selected patients with emphysema and with primary pulmonary hypertension. With single-lung transplantation, each of the lungs from a donor has been successfully used for a separate recipient on several occasions, improving the supply of available donor organs.

THE ELUCIDATION OF the basis for allograft rejection, by Sir Peter Medewar in the 1940s, laid the foundation for the development of organ transplantation. The famous Russian physiologist Demikhov successfully performed allografts of individual canine pulmonary lobes in 1947.¹ In 1950 Metras, in France, first published the technique of canine pulmonary allotransplantation.² He showed remarkable foresight because he described a technique of harvesting and anastomosing the left bronchial artery to provide systemic blood supply to the airway. In addition he described a left atrial anastomosis rather than separate pulmonary venous anastomoses. Hardin and Kittle,³ in 1954, also demonstrated the technical feasibility of lung transplantation in dogs,

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using a technique that has not changed substantially to the present time. Early experience with lung transplantation documented a deterioration of graft function causing the death of the recipient animal in approximately 7 days, a result attributed to rejection. Hardy⁴ observed that the duration of survival in dogs undergoing single-lung transplantation could be almost doubled by treatment with methotrexate, and survival could be further extended to a mean of 29 days if the animals were treated with azathioprine, or azathioprine plus steroids. After extensive laboratory investigation, Dr. Hardy performed the first human lung transplantation at the University of Mississippi in 1963.⁵ The donor lung was retrieved postmortem from a patient who had sustained cardiac arrest, and the recipient survived for 18 days, with death attributed to renal failure and malnutrition.

In the next 20 years, approximately 40 attempts at lung transplantation were made at many different centers, but no long-term clinical success was achieved. The only recipient to leave hospital, and the most notable success in this period, was a young man who received a lung transplant by Derom and colleagues.⁶ The initial 8 postoperative months were spent in hospital, with only a brief period of survival after discharge. Death was attributed to bronchial complications and infection.

Our initial attempt at lung transplantation, in 1978, resulted in death from bronchial dehiscence in the third postoperative week. A review of world experience at the time indicated that major complications relating to the bronchial anastomosis had occurred in 16 of the 20 patients who had survived more than 7 days after lung transplantation. Based on this review, and our initial experience, we embarked on a program in the laboratory to evaluate factors affecting bronchial anastomotic healing after lung transplantation. It was postulated that the failure in bronchial healing might be caused by a combination of factors, including ischemia of the donor bronchus due to transection of the bronchial artery supply, rejection, and the effect of immunosuppression, which, at the time,

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consisted of high-dose prednisone and azathioprine. It was confirmed that the routine use of high-dose steroids in the post-transplantation period seriously compromised bronchial healing.⁷ Cyclosporin could be substituted for steroids in the early post-transplantation period with significant improvement in bronchial healing.^{8,9}

Because clinical application of lung transplantation generally has not included revascularization of the bronchial arterial system, we evaluated the use of an omental pedicle wrap around the bronchial anastomosis at the time of transplantation. This restored bronchial circulation by means of collateral flow within several days and significantly reduced complications due to bronchial dehiscence and stenosis.^{10,11}

Based on this laboratory experience, a clinical program of lung transplantation was begun in 1983. We were encouraged by reports of successful combined heart-lung transplantation by the Stanford group¹² in patients with pulmonary hypertension and chronic right ventricular failure. In retrospect lung transplantation often had been applied in desperately ill patients, often in individuals who depended on a ventilator and who had multisystem failure, for whom transplantation was attempted as a death-bed rescue. Initially we chose to use lung transplantation in patients with end-stage pulmonary fibrosis. In such patients the native, remaining lung has markedly diminished compliance and increased vascular resistance so that ventilation and blood flow are preferentially directed to the transplanted lung. Such patients ordinarily do not suffer from chronic pulmonary sepsis, and thus the remaining lung does not pose an infectious risk. We selected the patients who were continuously dependent on oxygen and had demonstrated progressive deterioration in performance and pulmonary function during the preceding 12 months.

Patients selected for transplantation were those refractory to all forms of medical management, in whom the severity and progression of the disease, and increasing oxygen requirements, suggested a very limited life expectancy. Our initial transplant for pulmonary fibrosis was in a 58-year-old man whose transplant was performed in November 1983. This recipient recently died of renal failure 6.5 years after transplantation.

The experience with lung transplantation for pulmonary fibrosis has been gratifying. Of the initial 11 patients, nine survived the procedure and were discharged, with good performance and no oxygen requirement.¹³ An update of the initial 20 patients transplanted for restrictive lung disease was recently published.¹⁴ In this group there were four postoperative deaths. Of the remaining 16 patients, there were 5 late deaths, 3 from chronic rejection, 1 from lymphoma, and 1 from viral infection.

Initially we thought that unilateral lung transplantation was contraindicated in the presence of bilateral sepsis,

such as in cystic fibrosis. Furthermore we were concerned that unilateral lung replacement for chronic obstructive lung disease might lead to overexpansion of the native lung and crowding of the transplanted lung, in addition to a significant ventilation-perfusion mismatch. Such had in fact, been the experience with the 10 cases of single lung transplantation for obstructive lung disease reported between 1963 and 1983.¹⁵ Cognizant of the success achieved with the combined heart-lung transplantation in patients with right ventricular failure and pulmonary hypertension, we began to apply this procedure in patients with end-stage respiratory failure due to chronic obstructive or infective disease. In the course of this experience it soon became evident that such patients generally had adequate right ventricular function, and inclusion of the heart as part of the transplantation procedure was mandated primarily for technical reasons not because of physiologic necessity. In the laboratory a technique was developed for *en bloc* double-lung transplantation,^{16,17} a concept initially proposed by Vanderhoeft and co-workers¹⁸ in 1972. Clinical application of this procedure in the first seven patients was reported in 1989.¹⁹ In this initial series, there was one death and two complications as a result of airway ischemia, despite use of an omental pedicle wrap. Further experience with this procedure demonstrated a significant incidence of airway complications.²⁰ In an attempt to reduce airway complications after the double-lung transplantation procedure, two avenues of investigations were pursued. One method was to develop techniques for direct bronchial artery revascularization at the time of the transplant.²¹ The other was to use bilateral bronchial anastomosis rather than a tracheal anastomosis because retrograde bronchial artery flow from the lung to the airway becomes more tenuous the further the airway anastomosis is from the hilum of the lung. By using bilateral bronchial anastomoses, the incidence of airway complications after double-lung transplantation has been almost eliminated.²²

Advantages of the double-lung procedure compared to the combined heart-lung procedure for end-stage lung disease was associated with two distinct advantages: the recipient's heart is retained, thus avoiding both the short and long-term complications associated with cardiac transplantation; and the ability to use lungs from cardiac donors increases the supply of transplantable lungs. Results obtained with the double-lung transplantation procedure paralleled those achieved with heart-lung transplants, with a 1-year survival rate of 67%. With increasing experience, it was recognized that the double-lung transplantation procedure did have limitations: airway ischemia was a significant source of mortality and morbidity; the transplantation procedure is very complex and difficult to teach; extraction of infected lungs, such as in cystic fibrosis, can be associated with significant intraoperative

and postoperative bleeding problems because the lungs are extracted under conditions of total cardiopulmonary bypass; postoperative cardiac dysfunction, especially in recipients with preoperative right ventricular hypertrophy, occurs due to prolonged cardiopulmonary bypass and the need for ischemic cardiac arrest during the atrial anastomosis; postoperative exercise studies demonstrated some limitation due to a variable degree of cardiac denervation that occurs due to the mediastinal dissection. Postoperative exercise performance, while very satisfactory, thus showed some of the same limitations that have been reported in patients undergoing combined heart-lung transplantation.²³

To address these issues, the technique for bilateral lung replacement has been completely revised and a more simplified and satisfactory approach was developed. This new procedure uses the 'old-fashioned,' transverse, bilateral thoracosternotomy through the fourth or fifth interspace (Fig. 1). With this approach, superb exposure of both thoracic cavities from apex to diaphragm is provided. With unilateral lung ventilation, each lung can be completely mobilized, taking down adhesions, and isolating the hilar structures. Through an upper midline incision, the omental pedicle is prepared and split vertically into two pedicles, one for each side. The right lung is then excised and replaced in a fashion similar to that used for single-lung transplantation, while the patient is maintained with contralateral lung ventilation (Fig. 2). After replacement of the right lung, the recipient left lung is excised and replaced with the donor left lung (Fig. 3). Each bronchial anastomosis is wrapped with a separate omental pedicle. Depending on right ventricular function, the ischemic time of the donor lungs, and the stability of the recipient, tem-

porary low-flow cardiopulmonary bypass may be used during replacement of the left lung. This avoids diversion of the entire cardiac output through the newly transplanted right lung, and any associated strain on the right ventricle that might occur in the face of increased pulmonary vascular resistance. If a partial bypass is used for replacement of the second lung, this is easily accomplished by opening the pericardium and inserting a standard aortic cannula and a single left atrial cannula. Bypass flow of 1 to 2 L is used to maintain the systolic right pulmonary artery pressure at less than 30 mmHg. We have performed this procedure both with and without the use of cardiopulmonary bypass. Our initial experience recently was reported.²⁴ Our total experience with this procedure includes seven patients, with no deaths. All patients have excellent lung function after the procedure and in each case immediate postoperative PAO_2 on 100% oxygen has exceeded 500 mmHg, despite ischemic times of up to 9.5 hours for the second lung. At 24 hours after operation, all patients have had satisfactory blood gases on an inspired oxygen concentration of 30%.

Lung function and exercise performance have been excellent after this bilateral procedure. Because no mediastinal dissection occurs, there is no cardiac denervation with this procedure. Figure 4 demonstrates the preoperative and postoperative chest x-ray on a 31-year-old patient with cystic fibrosis who underwent this procedure. The pre- and postoperative pulmonary function data for this patient are shown in Table 1. We have used this bilateral procedure in two patients in whom exacerbation of chronic respiratory failure required intubation and ventilation for periods of 1 and 2 weeks, respectively, before the transplant procedure. We have been reluctant to extend the transplantation program to individuals with acute respiratory distress syndrome. However the bilateral transplantation procedure would seem well suited for such individuals if a transplant were to be considered.

At the same time that improved techniques for bilateral replacement have been developed, the indications for unilateral lung transplantation have significantly expanded. Following initial reports from France that unilateral lung transplantation had been successfully performed in several patients with emphysema,²⁵ we embarked on a program of single-lung transplantation for patients older than 50 years with end-stage emphysema for whom we thought the initial double-lung transplantation procedure was too complex. We have now performed 11 such transplants, with no hospital deaths and one late death due to an airway complication. As anticipated, a significant degree of ventilation to the native lung persists. The results of sequential ventilation and perfusion scans after single-lung transplantation for emphysema are shown in Figure 5. At six months ventilation to the transplanted lung has averaged 61%. This compares with 70%

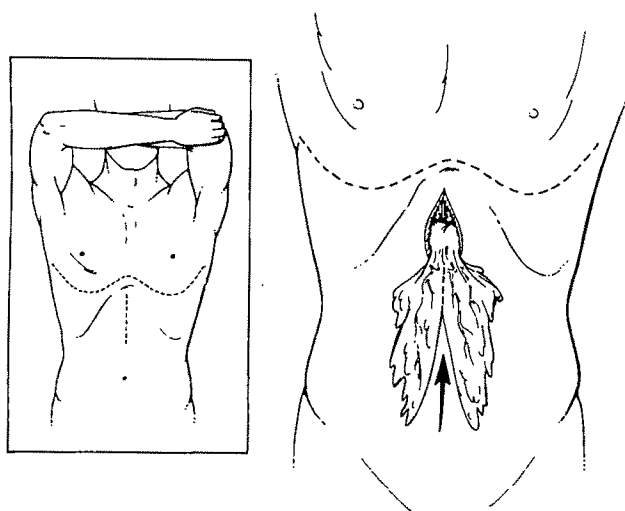
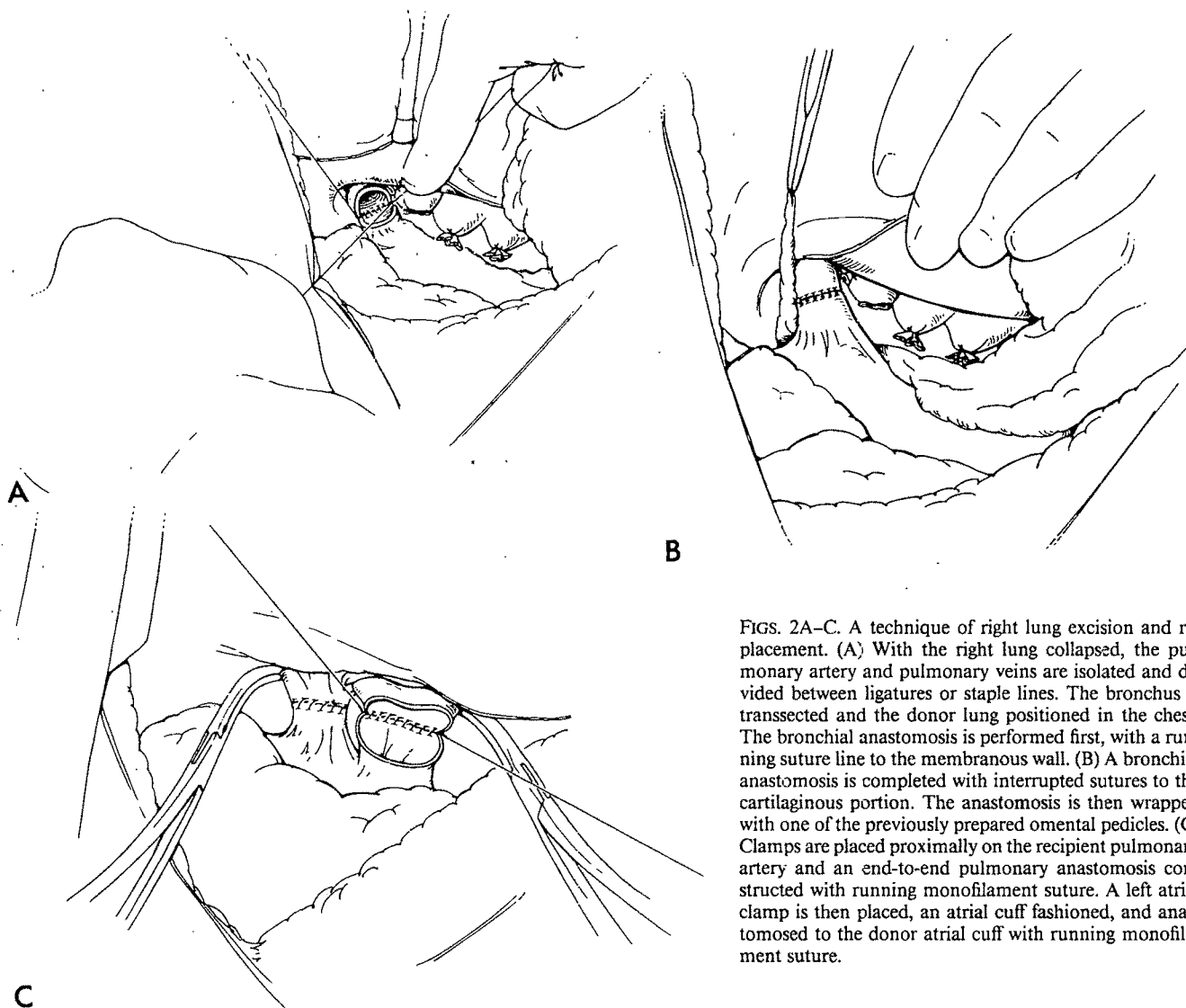


FIG. 1. The bilateral lung replacement is performed through a transverse thoracosternotomy incision using the fourth or fifth interspace. The arms are suspended above the face. An upper midline abdominal incision is used to mobilize the omentum and split it into two pedicles.



FIGS. 2A-C. A technique of right lung excision and replacement. (A) With the right lung collapsed, the pulmonary artery and pulmonary veins are isolated and divided between ligatures or staple lines. The bronchus is transected and the donor lung positioned in the chest. The bronchial anastomosis is performed first, with a running suture line to the membranous wall. (B) A bronchial anastomosis is completed with interrupted sutures to the cartilaginous portion. The anastomosis is then wrapped with one of the previously prepared omental pedicles. (C) Clamps are placed proximally on the recipient pulmonary artery and an end-to-end pulmonary anastomosis constructed with running monofilament suture. A left atrial clamp is then placed, an atrial cuff fashioned, and anastomosed to the donor atrial cuff with running monofilament suture.

ventilation to the transplanted lung for fibrotic lung disease. A report of our overall experience with single-lung transplantation for emphysema is in press.²⁶

Single-lung transplants recently have been used for selected individuals with primary pulmonary hypertension as an alternative to combined heart-lung transplantation. Single-lung transplantation for such individuals is predicated on two hypotheses: (1) that the transplanted lung must be able to receive virtually the entire cardiac output immediately, without development of pulmonary edema or other pulmonary dysfunction; and (2) that sufficient immediate recovery of right ventricular function must occur to avoid morbidity and mortality in the perioperative period as a result of right ventricular failure. An additional long-term consideration was the possible adverse physiologic affect of persistent ventilation to the contralateral lung in the absence of blood flow to that lung. To address the first issue, we obtained immediate postoper-

ative quantitative lung perfusion scans on patients undergoing single-lung transplantation for pulmonary fibrosis and found, in a number of instances, blood flow to the transplanted lung exceeded 80%, without apparent adverse effect. To address the second issue, that of right ventricular recovery, we conducted a series of experiments in dogs, with chronic pulmonary artery banding to produce right ventricular failure. Release of the pulmonary artery obstruction after a period of 3 to 6 months was associated with rapid recovery of right ventricular function.²⁷ This laboratory experience paralleled the clinical experience reported after pulmonary artery thromboendarterectomy for chronic pulmonary emboli and right ventricular failure.²⁸

We have performed right lung transplantation in three patients with primary pulmonary hypertension. The initial patient had systemic pulmonary pressures, despite continuous prostacycline infusion at the rate of 26 ngs/kg/

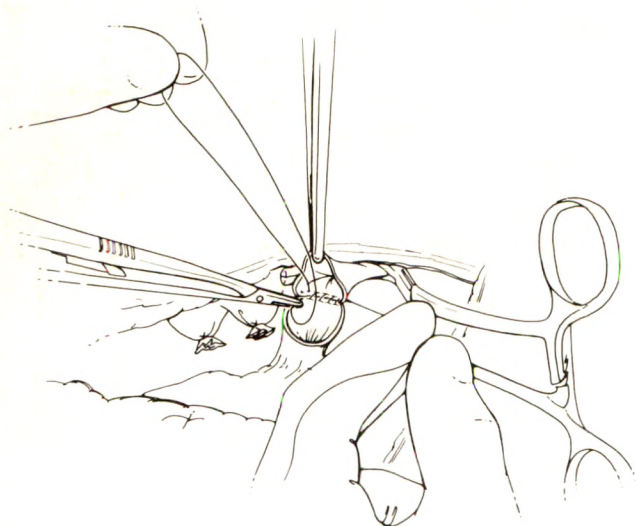


FIG. 3. Technique of left lung replacement. After replacement of the right lung, the left lung is excised and replaced in a similar fashion. In this drawing the bronchial anastomosis has been complete and the pulmonary anastomosis is being accomplished. Division of the ligamentum arteriosum allows the pulmonary artery clamp to be placed as proximal as possible on the left pulmonary artery.

minute. All three patients had depressed right ventricular function, patient 3 having a preoperative right ventricular ejection fraction of less than 10%. The right ventricular ejection fraction in this patient, immediately following right lung transplantation, improved to 40%. A quantitative lung perfusion scan obtained within hours of the transplantation procedure showed perfusion to the transplanted lung in excess of 90% in all three patients. Recovery has been excellent, with all patients having normal cardiac function on postoperative cardiac catheterization

TABLE 1. Bilateral Lung Transplantation for Cystic Fibrosis

Measurement	Preoperative	Postoperative
V.C.	1.69	3.90
FEV ₁	0.52	3.82
DLCO	12.5	22.8
R.V.	4.26	2.43
PO ₂	61.0 (3L)	72.0 (RA)

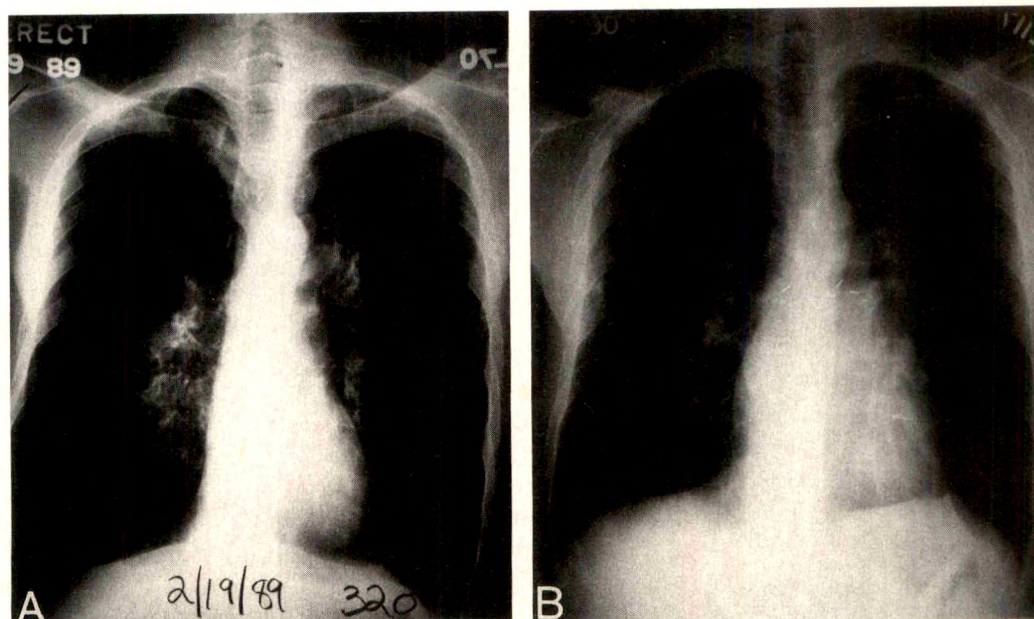
Pre- and postoperative (10 weeks) pulmonary function studies on a 31-year-old man undergoing a bilateral lung replacement for cystic fibrosis.

(Table 2). For reasons not clearly understood, long-term exercise tolerance in these patients has been excellent, with no apparent dyspnea or restriction of exercise capacity, despite persistent, significant ventilation to the native lung in the absence of perfusion to that lung.

Successful single-lung transplantation also has been reported successfully in individuals with primary pulmonary hypertension secondary to cardiac defects, such as patent ductus arteriosus and atrial septal defect.^{29,30}

A significant advantage of the single-lung transplantation procedure is the ability to use each of the donor lungs for separate recipients, a procedure we call 'twinning.' We have used it for two simultaneous transplants in our own institution, as well as for sharing of the donor lungs with other institutions.

Many problems still must be solved in the field of lung transplantation. Chief among them, perhaps, is the very limited availability of suitable organs for transplantation. This is caused not only by the general paucity of donors but also by the rapid deterioration of lungs after brain death. This is further complicated by often conflicting views on donor management by the various organ teams.



FIGS. 4A and B. (A) Before and (B) after chest x-ray on a 31-year-old man with cystic fibrosis. Bilateral lung replacement was performed using the transverse thoracosternotomy approach.

SINGLE LUNG TRANSPLANT FOR EMPHYSEMA

% Ventilation and Perfusion to Transplanted Lung

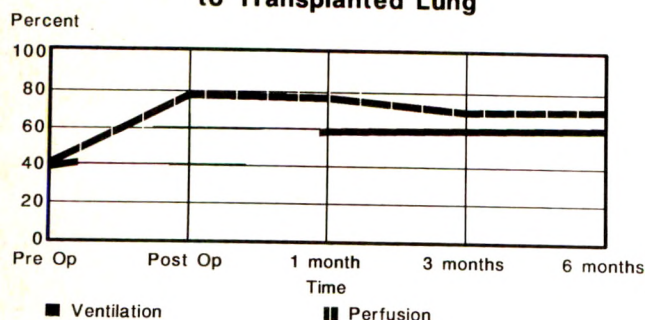


FIG. 5. Quantitative ventilation and perfusion scans in patients undergoing single-lung replacement for emphysema. In general the lung with the worst function is usually replaced, hence the preoperative values are less than 50% for the lung that is subsequently replaced. Ventilation to the transplanted lung averages 60% at 6 months. This compares with a mean of 70% in patients undergoing single-lung replacement for restrictive lung disease.

Retrieval of all satisfactory organs from a donor requires close cooperation and judicious management in terms of fluid administration, use of inotropic support, and overall donor management. Nonetheless, in a number of instances, lungs, heart, liver, kidneys, and pancreas all have been successfully transplanted from one donor.

Using current preservation techniques, which primarily consist of flushing of the lungs with cold electrolyte solution, an ischemic time of 6 hours is well tolerated. With the bilateral lung replacement technique, in which the ischemic time for the second lung is longer than the first, ischemic times of 7.5 to 9.5 hours for the second lung have been well tolerated. We have recently reported successful 12-hour lung preservation in a canine model using a low potassium-containing electrolyte solution.³¹ Currently, using a baboon model of bilateral lung transplantation, ischemic times of 12 and 14 hours for the right and left lungs, respectively, have been well tolerated with excellent postoperative lung function.

The diagnosis and treatment of both acute and chronic rejection remains a troublesome problem. The diagnosis

of rejection in the early postoperative period remains largely empiric, based on clinical findings, including temperature, diminishing PAO_2 , development of pulmonary infiltrates, and/or changes in quantitative lung perfusion scans. The routine use of transbronchial lung biopsies for the diagnosis of chronic pulmonary rejection has been valuable, especially in distinguishing between rejection and viral infection, such as cytomegalovirus (CMV) infection. Chronic rejection in the form of bronchiolitis obliterans has occurred frequently after combined heart-lung transplantation. This was not recognized initially after single- or bilateral-lung transplantation procedures, but with increasing experience several cases have been observed in such recipients. Whether the incidence of bronchiolitis obliterans will approach that observed following the combined heart-lung transplant procedure remains to be seen.

Techniques and indications for single and bilateral lung transplantation have evolved significantly in the past several years such that successful transplantation can now be achieved routinely, with success rates approaching those seen with other organ transplants. Using current techniques we have performed 24 single- or bilateral-lung transplants in the past 12 months, with no hospital deaths. There have been two late deaths, one due to CMV infection at 6 months in a patient transplanted for complications of chemotherapy for Hodgkin's disease, and the other due to airway complications 2 months after a single-lung transplant. As with other organ transplants, the major problems to be resolved include availability of suitable donor organs, improved immunosuppressive regimens, and the ability to promptly diagnose and effectively treat organ rejection.

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TABLE 2. Single-lung Transplant for Primary Pulmonary Hypertension: Cardiac Catheterization Data, n = 3

Measurement	Preoperative	Postoperative
PA (mean)	53	15
PVR	1130	198
RA pressure	5	0
C.O. (liters)	3.4	5.7

Pre- and postoperative cardiac catheterization data in three patients undergoing right lung transplantation for primary pulmonary hypertension. All patients showed normal cardiac function when restudied 3 to 6 weeks after the transplant.

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DISCUSSION

DR. FRANK J. VEITH (New York, New York): I think Dr. Cooper is to be congratulated for bringing this field to clinical fruition. As many of you know, we worked tirelessly in it for many years and presented a paper on single lung transplantation for emphysema with a clinically successful patient to this organization in 1973 (*Ann Surg* 178:463, 1973).

I think still the major problem in this field and the item that prompted us to withdraw from the field is the difficulty in procuring donor lungs. Many donors that are suitable for other organ transplantation still have diseased, infected lungs, and this is going to be the limiting factor in the clinical application of lung transplantation. Accordingly, we have developed a technique for procuring both lungs from the same donor after completion of a heart donation (*Surg Gynecol Obstet*, 166:363, 1988). Despite this, the donor problem remains.

DR. JOSEPH E. MURRAY (Boston, Massachusetts): Some 40 years ago when we started working on human and experimental renal transplantation at the Peter Bent Brigham Hospital and Harvard Medical School we noted that renal allografts in humans were not rejected as rapidly as skin allografts. It seemed surprising that a large vascularized whole-organ graft would elicit less immunologic response than a small postage-stamp-sized skin graft.

Accordingly we tried to identify on an *a priori* basis a hierarchy of organ antigenicity. We theorized that skin and lung would be the two most difficult organs to allotransplant because each had an epithelial surface exposed to the external environment and accordingly over the evolutionary ages had built up the greatest natural immunity to foreign proteins. To support this theory we noted that the two most common allergic conditions afflicting humans, that is, asthma and dermatitis, involve lung and skin.

At the other end of the immunologic spectrum we reasoned that heart and liver, derived from mesoderm and endoderm, would prove to be least antigenic, with the kidney somewhere in between.

Now that you have obtained a series of long-term lung allografts, are your rejection episodes less or more frequent and intense than for your liver and renal allografts?

DR. JOHN R. BENFIELD (Sacramento, California): One of the problems in the early days of lung transplantation was the differentiation of rejection from infection in the postoperative period (Benfield JR. Transplantation of the Lung. In Kirkpatrick CH, Reynolds HY, eds. *Immunologic and Infectious Reactions in the Lung*. New York: Marcel Dekker, 1976, pp 485-518). I think that it would be very helpful to us to hear how you accomplish this differentiation at present.

DR. HERBERT B. HECHTMAN (Boston, Massachusetts): I think you have the stick-to-itiveness that is really needed to not only do it, but to sell it to the audience.

Perhaps you can tell us what your current preservation techniques are and what the problems of reperfusion pulmonary edema are in your ischemic lungs.

DR. JOEL D. COOPER (Closing discussion): First, what a thrill to be sandwiched in between comments by Drs. Starzl and Hardy, and it is exciting to have Dr. Hardy in the audience. His first pioneering attempt followed many years of important laboratory investigation. We are all indebted to him as we are to Dr. Veith, who for many years in the dark ages kept the candle of hope flickering in this area. Had it not been for

his persistence, I think many of us wouldn't know anything about lung transplantation, and I am grateful as well for his kind remarks.

Also, Frank, I wish I had listened to you earlier about emphysema and not been quite as concerned as we were initially.

Dr. Murray, as usual, is right on target. As best we can tell, the lung is subject to more rejection than is seen in any of the other organs. Almost every patient goes through at least two or three major episodes in the first 3 weeks. And as you know, there is a persistent problem with some transplants of a more chronic form of rejection called bronchiolitis obliterans, so it is our impression that you are correct.

Dr. Benfield was also one of the very major contributors to the science of lung transplantation over the years, and Dr. Benfield, I am sorry to say that the clinical differentiation between rejection and infection and edema is still pretty much the flip of a coin. It is one of the things that I haven't learned how to teach because I am not quite sure how to do it. It is still based on a certain sense, the temperature, blood gases, x-ray, timing, and so on.

We are using transbronchial biopsies regularly. They are most helpful in distinguishing chronic rejection from viral infection such as CMV, but have not proven of particular benefit in the first 7 weeks, and I think that accurate diagnosis of rejection is one of the great challenges ahead.

Dr. Hechtman asked about preservation techniques. We use flushing of the lungs with a cold electrolyte solution, preceded by infusion of prostacycline, really much as has been done at Stanford.

We have gone out to 9.5 hours with good results.

I believe increasingly that what we used to call the reimplantation response, or the reperfusion pulmonary edema, is in fact related to poor preservation.

In the laboratory, using a low potassium electrolyte solution, we have a series of baboons who have had both their lungs replaced using the operation I showed you with 12 to 14 hours of ischemic time, and they have all shown excellent lung function, so I think if Dr. Starzl can keep these livers going for 24 hours with the UW solution, there is hope with lungs that we should be able to get out to 12 to 24 hours.

A Clinical Trial of Laser Thermal Angioplasty in Patients with Advanced Peripheral Vascular Disease

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A 3-year prospective trial of laser thermal-assisted balloon angioplasty in 28 patients included 27 who had advanced peripheral vascular disease (severe tissue loss, gangrene, infection, and rest pain), 7 who were failures of previous therapy (surgery and thrombolysis), and 4 who were high risk for operation (myocardial infarction within 6 weeks and/or ejection fractions of $\leq 20\%$). Laser angioplasty was performed in the operating room *via* a groin incision by a surgeon-radiologist team. In the 27 patients with advanced peripheral vascular disease (ankle-brachial systolic pressure index [ABI] 0.27 ± 0.2 in 10 nondiabetic, and 0.46 ± 0.1 in 17 diabetic patients), recanalization of the native vessel was successful in 16, and patency was restored in 2 chronically occluded polytetrafluoroethylene (PTFE) grafts. In these 18 (67%) successfully recanalized patients, however, five amputations were required within 1 month, and another six were needed between 8 and 12 months. Early amputations were caused by a failure of wound healing, even though angioplasty sites were patent. Late amputations were caused by reocclusion of the treated site in five of six patients. In the remaining seven patients in whom laser angioplasty alone was successful, five have healed limbs at 6 to 24 months and two remain incompletely healed but functional. The patency for successful procedures ranged from 48 hours to 25 months (5.6 ± 6.4 mean months, $\pm$ SD), with cumulative patency by life-table analysis of 55.5% at 3 months, 38.8% at 6 months, and 11.1% at 12 months. There were no procedure-related deaths. Complications included seven arterial wall perforations by the laser probe. We conclude that laser angioplasty has a limited role in advanced peripheral vascular disease but may provide an interval patency, thus allowing postponement of operation for high-risk patients until their medical conditions permits surgery, or to correct local tissue necrosis or infection in the operative field before reconstruction, and to restore patency to thrombosed PTFE grafts.

LASER ANGIOPLASTY IS a controversial modality with regard to both immediate efficacy and long-term durability. Optimistic reports have been based on laser thermal treatment of stenotic segments or short, arterial occlusions.^{1,2} In these studies, lasers have been used as a thermal source or as unguided free energy to recanalize the artery. So far only limited applications have been identified that go beyond those of conventional surgical procedures or available devices, such as transluminal balloon angioplasty.³⁻⁶

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Atherosclerotic lesions treated by endovascular surgical instruments often do not meet the criteria for surgical reconstruction. Short segmental occlusions or stenoses of the superficial femoral or iliac arteries have been treated in patients in whom early claudication and absence of limb threat would not warrant bypass operation. If benefit is to be derived from endovascular intervention, the technique must be developed to a point at which complex lesions producing symptoms that would require surgery can be treated successfully. Enthusiasm for endovascular devices is understandable given the minimal intervention through a percutaneous insertion or a small incision, which promises the same benefit as an operation but without the morbidity.

Our study evaluated the efficacy of laser thermal-assisted balloon angioplasty (LTABA) in the treatment of patients with advanced peripheral vascular disease and in high-risk patients who were poor candidates for operative reconstructions. These patients would benefit most from the minimal intervention of endovascular techniques because they have the highest rates of mortality and complications from operations.

Patient Data

Twenty eight patients (13 men, 15 women; age range, 48 to 82 years; mean, 61 years) who had advanced peripheral vascular disease and/or were considered high-risk for surgery were entered into a 3-year prospective study that evaluated LTABA as initial therapy. Twenty-seven individuals had severe peripheral vascular disease (ankle-brachial systolic pressure index [ABI]; 0.39 ± 0.17 , mean $\pm$ SD; $n = 24$), including 21 limbs with tissue loss and/or infection (ABI, 0.37 ± 0.18 ; $n = 19$). Using suggested standards for reports dealing with lower-extremity ischemia,⁷ the 21 patients with tissue loss were classified as grade III, category 5; six with ischemic rest pain were grade III, category 4; and one severe claudicator was grade I, category 3. Eight patients in this group were failures of previous multiple surgeries ($n = 7$) or thrombolysis (n

= 1). Four of the 28 patients were high risk for operation because of a myocardial infarction within 60 days ($n = 2$) and/or a left ventricular ejection fraction $\leq 20\%$ ($n = 2$).

Laser thermal-assisted balloon angioplasty was performed in the operating room in all patients using local or epidural anesthesia. Most patients were treated by a combined surgery-radiology team. The iliac or femoral artery was approached *via* a groin incision slightly smaller than one used for femoropopliteal bypass in 26 patients, while the laser devices were used *via* an 8-French hemostatic introducer placed using percutaneous Seldinger technique in two patients. After successful angioplasties, the groin wounds were drained and closed and heparin 1000 U/hour was continued intravenously for 24 to 48 hours after operation. Following discontinuation of the heparin, all patients were given aspirin (60 mg/day). One patient with a recanalized polytetrafluorethylene (PTFE) graft was treated with Coumadin (DuPont, Wilmington, DE) for 11 months. Unsuccessful laser recanalizations were followed immediately by conventional reconstructive procedures when possible (seven of nine patients).

Outcome of the procedures were determined using the Society for Vascular Surgery/International Society for Cardiovascular Surgery (SVS/ISCVS) criterion for significant change in status of the treated limbs.^{7*} All patients entered signed an informed consent to enroll in the protocol approved by our institution's Research and Human Subjects Committees.

Clinical Devices and Methods

The laser devices used included both experimental and Food and Drug Administration (FDA)-approved probes that became available during the study interval. The laser-thermal probes included 2.0-, 2.5-, and 3.5-mm SLR† (Surgical Laser Recanalization^R; $n = 20$) probes that have solid metal caps and are solely thermal instruments. In addition 2.0- and 2.5-mm Spectraprobes^R,† which emit approximately 18% of the laser energy from a window at

the tip of the metal probe, were also used ($n = 5$). Laser Recanalization (LR) or Flex probes, which have 2.5-, 3.0-, 3.5-, and 4.2-mm eccentric football-shaped tips that are trackable over a 0.32- or 0.35-inch guidewire were used to further enlarge the lumen and help prevent perforations ($n = 8$). An additional device, a 1.7-mm Lasercath^R,† which has a rounded tip and a central 0.14-inch guidewire channel, also was used in one patient. Both argon (Optilase^R†) and Nd:YAG (Cardiolase^R†) lasers were used to energize the probes. Initial laser-thermal recanalizations were enlarged by passing serially larger probes over a wire or by balloon dilatation. Adjunctive balloon passage was not possible in four patients.

Angioscopy was performed on all treated arteries before and after angioplasty. Angiograms were routinely performed on all repairs and selected vessels had intraluminal ultrasound evaluations. When possible specimens from failed procedures, *i.e.*, perforations or unsuccessful recanalizations, were removed for histologic examination at a concomitant reconstruction subsequent to an unsuccessful attempt or at the time of an amputation. These specimens were used to correlate the angiographic, angioscopic, and intraluminal ultrasound examinations with the morphologic data obtained. Patients were followed by clinical examination, ABI, and arteriography if reocclusion was suspected.

Results

Success of Initial Recanalizations

In the 27 patients with advanced peripheral vascular disease, ABI values before intervention were 0.27 ± 0.2 in 10 nondiabetics and 0.46 ± 0.1 in 17 diabetic patients. Recanalization of occlusions (4 to 24 cm; 11.2 ± 6.1 cm, $n = 13$) and three diffusely stenotic and occluded native infrainguinal arteries was successful in 16 vessels (59%). In two additional patients, patency was restored to chronically occluded PTFE grafts after perforations of the superficial femoral arteries, improving the primary recanalization using LTABA alone to 67%. Of the nine patients (33%) who had unsuccessful LTABA recanalizations, seven had bypasses or endarterectomies performed immediately after the angioplasties during the same surgical procedure.

Postoperative Course

In the 18 successfully recanalized patients (Table 1), five amputations were required within 1 month of the procedure and another six were needed between 8 and 12 months. Early amputations were caused by failure of healing of tissue necrosis, even though three of the four angioplasties were patent. The fifth early amputation occurred as a result of a multiple emboli from a concomitant iliac artery dilatation. Late amputations were caused by

* Ad Hoc Committee of the Society for Vascular Surgery/North American Chapter, International Society for Cardiovascular Surgery.

+3 = Markedly improved: symptoms gone or markedly improved; ABI increased to more than 0.90.

+2 = Moderately improved: still symptomatic but at least single category improvement; ABI increased by more than 0.10 but not normalized.

+1 = Minimally improved: more than 0.10 increase in ABI but not categorical improvement, or vice versa (*i.e.*, upward categorical shift without an increase in ABI of more than 0.10).

0 = No change: no categorical shift and less than 0.10 change in ABI.

-1 = Mildly worse: no categorical shift but ABI decreased more than 0.10 or downward categorical shift with ABI decrease less than 0.10.

-2 = Moderately worse: one category worse or unexpected minor amputation.

-3 = Markedly worse: more than one category worse or unexpected major amputation.

† Trimedyn, Inc., Santa Ana, CA.

TABLE 1. Clinical Data on 18 Patients with Advanced Peripheral Vascular Disease Having Initially Successful Recanalizations with LTABA (All Grade III, Category 5 or Grade II, Category 4^a Limb Ischemia)

Age	Sex	Site Treated	Duration of Patency (months)	No. Withdrawn Due to:		Outcome*	Comments
				Surgery	Death or Lost to Follow-up		
54	F ^a	12 cm SFA and popliteal artery occlusion	2 days	<i>in situ</i> ; patch distal <i>in situ</i> stenosis ×2 at 6-month intervals, BK	Death at 16 mo.	0	Lupus antibody, AKA of contralateral extremity for progressive thrombotic occlusions
68	M	10-cm popliteal artery occlusion, 90% anterior tibial as only runoff	5 days	BK; angioplasty patent		0	Hip osteomyelitis; 6 years s/p <i>in situ</i> ; 6 months s/p coronary bypass
54	M	12-cm popliteal artery occlusion	8 days	<i>in situ</i> ; BK		0	<i>In situ</i> at 4 days for no improvement
55	F	15-cm SFA and popliteal artery occlusion	8 days	AK		0	Occlusion of femoral artery percutaneous insertion site at 4 days and <i>in situ</i> performed
60	F	7-cm SFA occlusion	14 days	Femoropopliteal bypass 4 months following angioplasty		0	Poorly healing ulcer at 9 months
56	F	10-cm SFA occlusion	18 days	BK, angioplasty patent		0	BK revised to AK
48	F	80% iliac artery stenosis, 6-cm SFA occlusion	21 days	AK		-3	SFA LTABA successful; trash limb from iliac artery balloon dilatation
56	M	Popliteal artery occlusion, no vessels in continuity to foot	2	Fem-pop at 4 months; AK at 8 months following failure of <i>in situ</i> ×2		+1	High risk-3 weeks s/p myocardial infarction
61	F	4-cm SFA occlusion	3		Lost to follow-up at 3 months	+1	Improved with foot healed at 3 months follow-up
62	M	3-cm SFA	4	Femoropopliteal for tight restenosis with transmetatarsal amp; BK 4 months later		0	
66	M	15-cm SFA and popliteal artery occlusion	5	BK		+1	Four previous leg bypasses or revisions
65	F	20-cm SFA diffuse stenosis	6		Lost to follow-up at 6 months	+2	Foot healed ABI 1.1 at 6 months follow-up and returned to El Salvador
56	F	20-cm SFA occlusion; PTFE graft occluded for 1 year	8	Femoropopliteal below knee thrombectomy ×2 at 3 months; BK		+2	Successful recanalization of PTFE graft
59	M	4-cm SFA occlusion	9	BK		+2	BK at 9 months performed for cellulitis and sepsis
52	M	24-cm SFA occlusion	10			0	Persistent draining toe at last follow-up
69	F ^a	17-cm SFA occlusion	11			+2	Three previous fem-pops (1 vein, 2 PTFE); PTFE recanalized; thrombophlebitis post op.
70	M	Discrete 60% common femoral artery stenosis, 20-cm SFA occlusion	13	Femoropopliteal 17 months after LTABA		+2	High risk; 8 wks s/p myocardial infarction
60	M	15-cm diffuse SFA stenosis	25			+2	Femorofemoral and femoropopliteal bypasses to contralateral leg after angioplasty

* Outcome criterion for significant change in status following the procedure described by Rutherford et al.⁷

^a Patients classified as grade II, category 4.
SFA, superficial femoral artery; LVEF, left ventricular ejection fraction.

reocclusion of the artery in all but one instance. In the remaining seven successful cases, five have healed limbs at 6 to 24 months and two remain unhealed (one after femoropopliteal bypass). The patency for successful procedures ranged from 48 hours to 25 months (5.6 ± 6.4

months, mean $\pm$ SD), with cumulative patency by life-table analysis of 55.5% at 3 months, 38.8% at 6 months, and 11.1% at 12 months.

Of the nine patients who had unsuccessful laser recanalizations (Table 2), six had patent bypasses or endarter-

TABLE 2. Clinical Data on Nine Patients with Advanced Peripheral Vascular Disease Having Initially Unsuccessful Recanalizations with LTABA (All Grade III, Category 5 or Grade II, Category 4^a Limb Ischemia)

Age	Sex	Site Treated	Duration of Patency (months)	No. Withdrawn Due to		Outcome*	Comments
				Surgery	Death or Lost to Follow-up		
75	F	90% diffuse lesions of SFA	—	AK		0	Recanalization but subsequent guidewire perforation
82	F	Diffuse SFA lesions, popliteal artery occlusion	—	<i>In situ</i> bypass to distal popliteal		+2	Ambulatory, claudication with graft patent at 2 years
53	F	Thrombosed aorto-bifemoral graft; 10 cm SFA occlusion	—	BK		0	Aortobifemoral graft thrombectomy and SFA perforation
55	M	Iliac artery 10 cm occlusion	—	Aortobifemoral bypass		+1	Iliac artery guidewire perforation, fem-pop 1 mo following aortobifemoral bypass
71	F	3 cm left iliac artery and SFA occlusion	—	Wire dissection, retroperitoneal iliac endarterectomy		+2	High risk-s/p left CVA with weakness; LVEF 18%
51	F	5 cm distal SFA occlusion	—	<i>In situ</i>		+1	Introducer dissection proximal SFA, perforation distal SFA
56	F	6 cm posterior tibial artery occlusion	—	<i>In situ</i> to distal posterior tibial artery	Death 43 days after BK amputation	0	Lasercath recanalization, Judkin's catheter perforation, compartment syndrome
75	M*	12 cm SFA	—	Above-knee PTFE bypass	Death at 14 mo.	+1	s/p 3 toe amputations with persistent infections at death
77	F*	15 cm SFA occlusion	—	<i>In situ</i>	Lost to follow-up at 4 mo.	+2	Rest pain resolved, foot healed

* Outcome criterion for significant change in status following the procedure described by Rutherford et al.

^a Patients classified as grade II, category 4.

SFA, superficial femoral artery; LVEF, left ventricular ejection fraction.

ectomies at 3 to 24 months, but three of these had persistent problems with wound healing (Table 2). The three remaining patients in this group had amputations within 2 months after unsuccessful simultaneous surgeries.

An example of the potential utility of the laser angioplasty methods is demonstrated by the following case report.

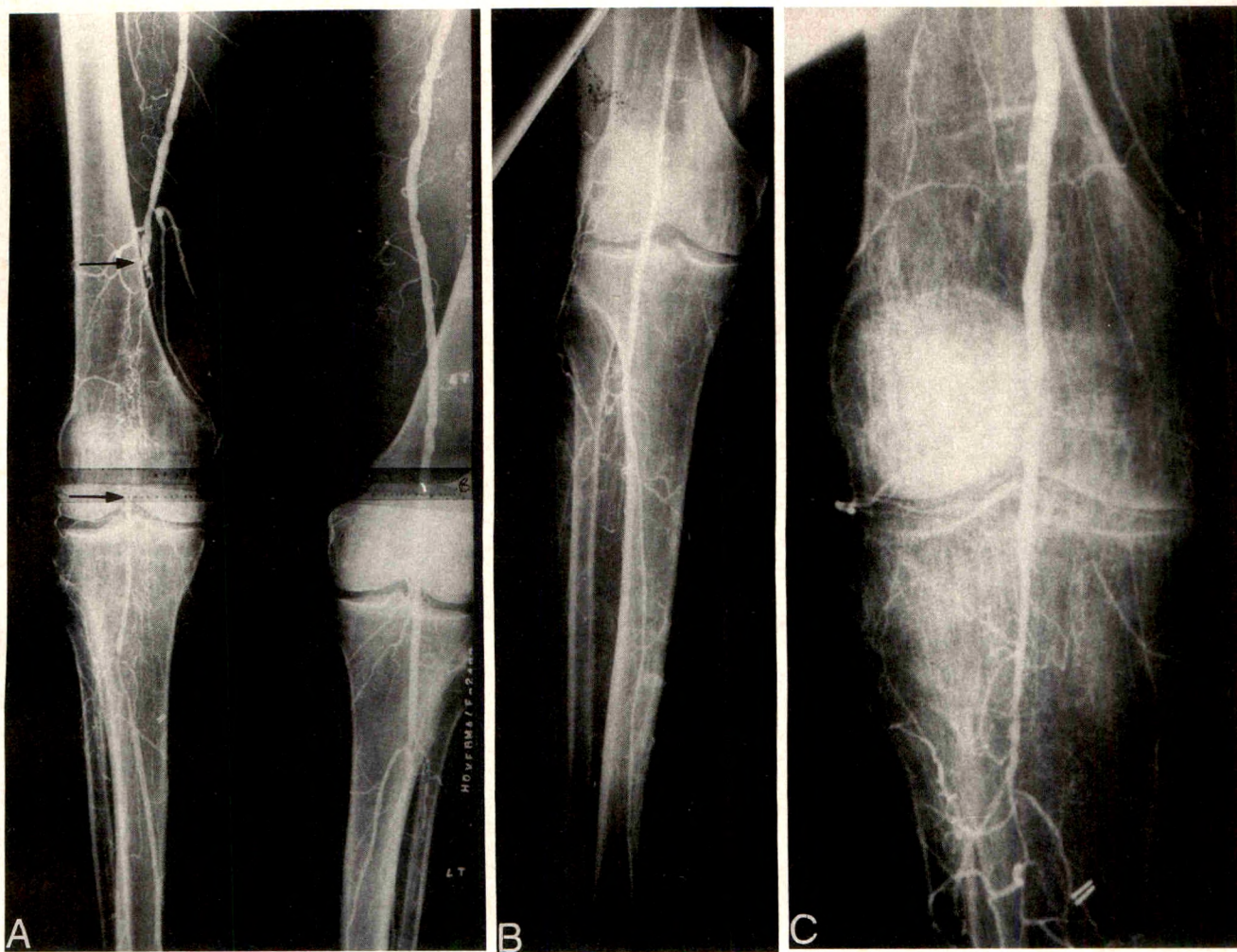
Case Report

A 63-year-old man who walked with a cane had rest pain, infection of two toes, a nonhealing ulcer, and ABI ratio of 0.25 in the right leg. The right hip was fused after an injury and had a chronic, draining osteomyelitis. Six years earlier an *in situ* bypass salvaged the right limb but had recently occluded, precipitating the present symptoms. The saphenous veins had been used for coronary artery bypasses 6 months previously. Angiography demonstrated a 10-cm occlusion of the popliteal artery and a discrete lesion at the origin of the anterior tibial artery, which was the only vessel patent to the foot (Fig. 1). At operation the popliteal artery was successfully recanalized with a 2.5- and 3.5-mm SLR probe and dilated with a 5.0-mm balloon. The tibial lesion was dilated with a 3.0-mm balloon, thus restoring flow to the foot and increasing the ABI to 0.50. Angiography at 1 year, done in conjunction with angioplasty of an iliac lesion, demonstrated the patency of the laser thermal-treated sites.

The four high-risk patients in this study were treated following myocardial infarctions or had ejection fractions $\leq 20\%$ (Table 3). Two patients had interval patencies accomplished by the lesser procedures of 4 and 13 months before reocclusion, allowing femoropopliteal bypass to be

performed at a safer time after myocardial infarctions. One patient with an ejection fraction of 18% and non-healing wounds had a wire dissection of the iliac artery treated by retroperitoneal endarterectomy and subsequently healed the lesions. The fourth patient was a 52-year-old man who had severe claudication with occasional rest pain (grade I, category III), chronic obstructive pulmonary disease, a history of two myocardial infarctions within the last 8 months, and an ejection fraction of 20%. A left iliac artery occlusion could not be crossed by a wire but was recanalized by a Spectraprobe[®] and dilated with a balloon. This patient is ambulatory without leg pain 7 months later (Fig. 2). The preoperative ABI of 0.4 improved to 0.75.

Angioscopic inspection of the angioplasties following recanalizations revealed wall charring and thermal effects, plaque cracking, intimal flaps, and fragmentation of lesions in most of the treated segments. These defects were underestimated on intraoperative angiography and large flaps and thrombus were removed endoscopically in three patients. Intravascular ultrasound images of the treated vessels complemented the angioscopic views of the intraluminal surfaces by providing a transmural image of the vessel wall and residual lesions. Histologic sections obtained from failed procedures following perforations of the vessel wall or at amputations or during reconstructions at various intervals after the initial procedures revealed



FIGS. 1A–C. (A) Preoperative angiogram demonstrating occlusion of the superficial femoral artery (arrows) with reconstitution of a high-grade stenosis of the origin of the anterior tibial artery that is the only runoff vessel to the foot. (B) Angiogram of the recanalized superficial femoral segment following LTBA, and (C) angiogram 1 year after recanalization demonstrating continued patency of the popliteal artery.

that passage of the devices through eccentric channels in the atherosclerotic vessel lumen predisposed to subintimal dissections and perforations.

Complications

The most frequent complication in this series was perforation of the vessel wall (11 of 28 walls, 39%). Seven (25%) of the perforations were caused by the laser probe and four (14%) were related to guidewires or balloon dilations. Three additional artery dissections were produced by either wires or introduction catheters at the arteriotomy site but were repaired by local endarterectomy when the vessel was closed at the conclusion of the procedure. Most of the perforations sealed without consequence. Two of the perforations of the superficial femoral artery produced an arteriovenous fistula with the femoral vein. Both fistulas closed without further therapy. One patient (who had had an arteriovenous fistula) developed deep-vein phlebitis and required hospitalization, antico-

agulation for 7 days, and had persistent limb swelling for approximately 6 months after discharge. One perforation at the bifurcation of the tibioperoneal trunk resulted in a compartment syndrome after operation and the patient was returned to surgery for femoroposterior tibial *in situ* vein bypass.

Discussion

Clinical evaluation and development of laser technology has been limited. The first feasibility studies of angioplasty, performed in the early 1980s, showed that plaque ablation may be achieved by the intraluminal application of laser energy but that imprecise delivery and thermal injury caused a high rate of vessel-wall perforation.⁸ The tissue penetration and thermal injury were related to characteristics of the first continuous wave argon and Nd:YAG lasers available for the operating room. An ovoid metal cap was attached to the end of the fiberoptic bundle to confine the thermal effect. Known as the 'hot

TABLE 3. Clinical Data on Four High-risk Patients Treated with LTABA (All Grade III, Category 5 or Grade I, Category 3^a Limb Ischemia)

Age	Sex	Site Treated	Duration of Patency (months)	No. Withdrawn Due to		Outcome*	Comments
				Surgery	Death or Lost to Follow-up		
71	F	3 cm left iliac artery and SFA occlusion	—	Wire dissection retroperitoneal iliac endarterectomy		+2	L. CVA with weakness; LVEF 18%
56	M	Popliteal artery occlusion, no vessels in continuity	2	Femoropopliteal at 4 months, AK at 8 months after failure of <i>in situ</i> ×2		+1	3 weeks after myocardial infarction
70	M	Discrete common femoral artery stenosis, 20 cm SFA occlusion	13	Femoropopliteal at 17 months after LTABA		+2	8 weeks after myocardial infarction, LVEF 20%
52	M ^a	5-cm iliac artery occlusion	7			+2	2 myocardial infarctions in last 8 months; LVEF 20%

* Outcome criterion for significant change in status after the procedure described by Rutherford, et al.⁷

^a Patients classified as grade I, category 3.

SFA, superficial femoral artery; LVEF, left ventricular ejection fraction.

tip,' this concept arose as a method to capture and enhance thermal tissue ablation of the continuous-wave laser systems.

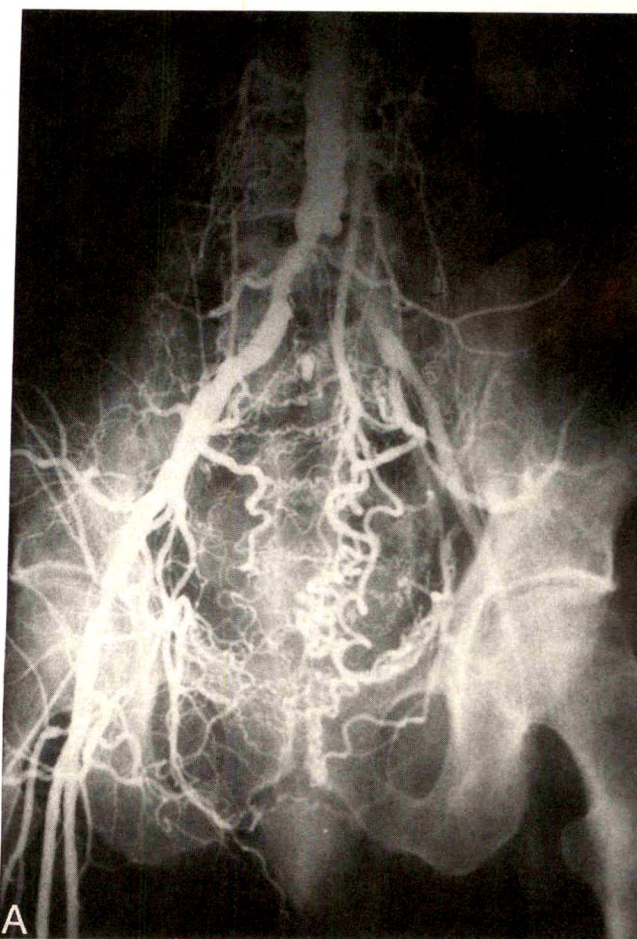
The initial clinical evaluations of the laser-thermal angioplasty systems used 1.5- and 2.0-mm diameter hot tips on a 600- μ m fiberoptic. These studies were designed to compare the efficacy and safety of the technique to the conventional, approved balloon angioplasty methods. Approximately 60% of the procedures were done for stenotic femoropopliteal arterial lesions, a low-risk site for preliminary studies, but no comparison was made to operative procedures. Patients had relatively early disease; for example the ABI values of successfully treated occlusive lesions were 0.53 ± 0.17 before the procedure.⁹ Because the laser probes create a channel that is smaller than the size of the metal cap (channel size is estimated to be 60% to 70% of the tip diameter), the initial recanalizations were followed by balloon dilatation to further enlarge the lumen. Thus this technique is correctly called laser thermal-assisted balloon angioplasty.

Impressive preliminary reports of successful recanalizations fuelled optimism regarding the utility of laser-thermal devices. A multicenter experience with 219 peripheral arteries in 10 institutions¹ gained FDA approval in March 1987 of the 1.5- and 2.0-mm LTABA devices for iliac and femoropopliteal artery lesions. The approval was based on the initial angiographic and clinical success (155 [71%] of 219 attempted lesions) with the lesions categorized subjectively by the angiographer into those considered possible or impossible to treat by conventional balloon angioplasty. The 1-year clinical patency of 77% of 99 successfully treated lesions from two of the centers (Boston University, Boston, Massachusetts and Northern General Hospital, Sheffield England) is comparable to representative reports of patency for balloon angioplasty.²

From these early studies it appeared that the combined LTABA technique was applicable in a higher percentage of cases compared to balloon angioplasty alone and that the method could recanalize a higher percentage of long-

segment occlusions. The complication rates, including vessel perforations, groin hematomas, and so on, were about 6% to 10% and the incidence decreased with experience.

Increase in the size of the initial channel created by the probes was attempted by investigating larger probe sizes



FIGS. 2A and B. (A) Abdominal demonstrating 5-cm occlusion of the left iliac artery, and (B) Patency of the vessel following transluminal LTABA.

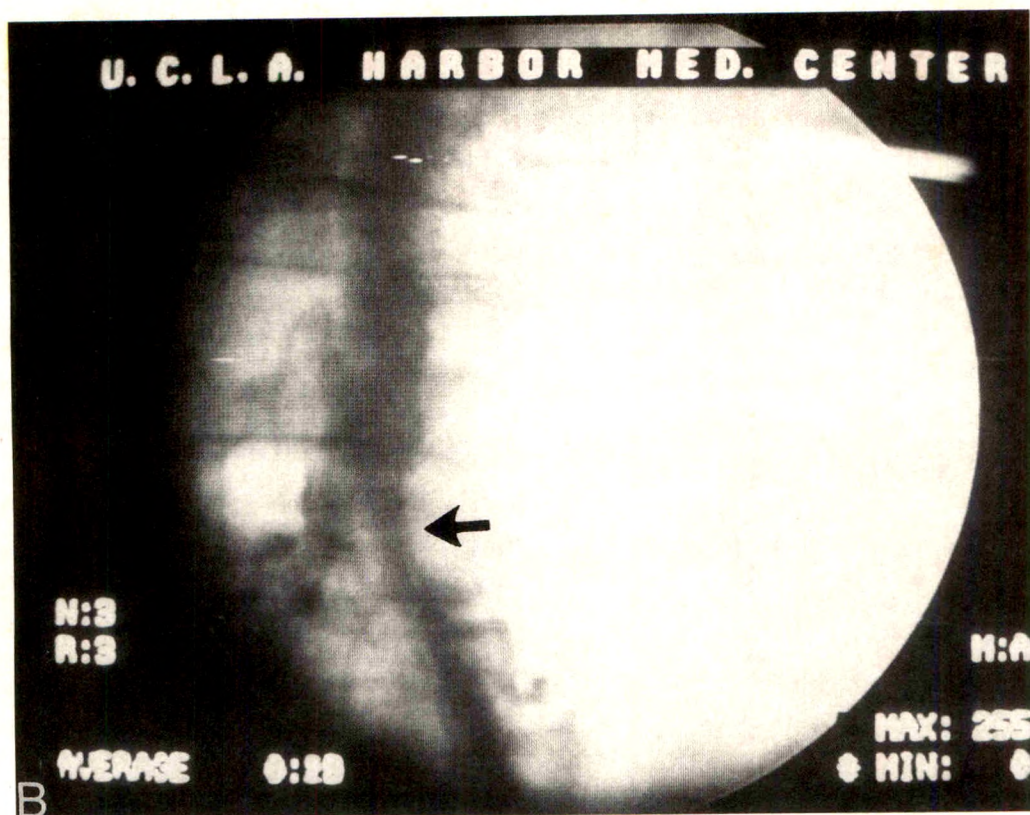


FIG. 2. (Continued).

included 2.5-, 3.5- and 5.0-mm diameters. The 2.5-mm probe was approved for use in October 1987 and was the most commonly used probe after its FDA approval. The hybrid probe was developed to provide better forward ablation of tissue by partial emission (approximately 20%) of the 'free' laser energy combined with the metal-tip thermal effect. Rapid evolution of the laser-thermal devices and introduction of the controlled energy emission *via* the 'hybrid' concept or Spectraprobe^R saw the use of multiple probes and guidewires during an angioplasty procedure.

As surgeons and radiologists began to use these devices in longer occlusions in patients with conventional indications for surgery, the reported incidence of arterial wall perforations, reocclusions, and early restenosis increased dramatically.^{5,10,11} The rapid evolution of technology, consumer and media interest, and multiple subspecialty application (cardiologists, radiologists, and surgeons) for differing indications, combined with a significant economic impetus for use and development, makes laser angioplasty a highly controversial issue.

Disobliteration of occluded arteries *via* an endoluminal approach was one of the first methods devised by vascular surgeons. An endarterectomy was performed by various means, such as introduction of strippers or gas, enabling removal of the entire lesion through a small arteriotomy. Radiologists and cardiologists focused primarily on enlarging the vessel lumen by dilating the vessel, compacting

the lesions, or lysing easily soluble constituents. The long-term efficacy of either approach is limited by recurrence of the lesions.¹² Comparing the two methods, endarterectomy yields a more durable repair with recurrences reported at 30% to 60% at 5 years for superficial femoral artery lesions,¹³⁻¹⁶ while balloon dilatation restenosis is 20% to 40% at 1 year in the same location.

Many surgeons are skeptical of the value of endovascular angioplasty devices, believing that the patency rates reported for endarterectomy represent the best estimate of the potential for the new technologies and are inadequate when compared to patencies obtained from reconstructive operations. Achieving long-term patency of 'endarterectomylike' endovascular recanalizations awaits a solution to the control of more fundamental cellular mechanisms causing recurrences. Nevertheless short-term patency obtained with minimal intervention may be beneficial in selected patients.

This study evaluated the efficacy of LTABA, a method with potential to accomplish endovascular endarterectomy, in patients who had severe peripheral vascular disease. Twenty-one of twenty-seven patients (77%) had tissue necrosis and infection in the distal limb, and 16% were high-risk candidates for surgery. Current epidemiologic data regarding this type of patient suggests a 50% or greater mortality rate within 5 years from associated illnesses.¹⁷ These patients also have a significant risk for both reconstructive surgery and for amputation.¹⁸ A con-

cept under trial in this study was that a minimal intervention, which could be repeated at an interval projected to be that of the recurrence rate of endarterectomies, would provide an alternative therapy in these difficult clinical cases.

Other studies of LTABA in patients with disabling claudication and limb threat have obtained similarly low clinical success and patency rates. Wright¹⁰ reported patency of successfully treated superficial femoral arteries as 25% at 6 months in limb salvage. Perler¹¹ noted a 29% cumulative patency at 1 year among successfully lasered vessels in a better-risk group (78% claudicators). These results are consistent with our findings of 38.8% patency at 6 months and 11.1% at 1 year.

Our study suggests a limited potential of LTABA to gain interval patency and identifies the mechanisms of failure. We were disappointed that even when LTABA established patency, areas of tissue necrosis did not heal, whereas this often occurs with bypass operations. Laser thermal assisted balloon angioplasty may treat too limited a site in patients with multiple lesions, while bypasses encompass a greater length of diseased vasculature. Only partial removal of arterial lesions as demonstrated by angioscopic, ultrasound, and histologic evaluation following the procedures obviously limits the hemodynamic result.

The 39% perforation rate in this study is higher than reported by some investigators, probably because of the severity and length of occlusive disease, and because all patients gave consent for alternative reconstructions, if possible, so we were more persistent in attempts at recanalization. In many studies, follow-up data frequently eliminates evaluation of these failures in statistical analyses. The limited utility and significant complication rate of current angioplasty devices, including the laser thermal probes discussed in this paper, argues for evaluation and further development of the methods by surgeons where the option for immediate intraoperative repair of failed recanalizations is possible.

Analysis of the outcome in our patients demonstrates that there is a limited role for LTABA in advanced peripheral vascular disease. The majority of patients did not have the predicted clinical course of severe atherosclerotic arterial disease altered significantly by the use of this technology as the initial therapy. Chronically thrombosed PTFE grafts may be restored to patency for 8 to 12 months, or possibly for longer periods by hemodynamic monitoring and repeat procedures before reocclusion occurs. Perhaps the most important potential gain is an interval patency in patients who are at high risk for bypass surgery by delaying reconstruction to a more favorable time.

Laser-powered thermal devices represent only an early phase in the development of the full potential of controlled free laser energy for angioplasty. Newer laser instruments are returning to the free light principle with some using

the convenient argon and the Nd:YAG continuous-wave laser systems. One of the most promising techniques for precise nonthermal or limited thermal ablation is high-energy pulsed laser delivery, which can recanalize more resistant, calcified lesions.^{3,4,19} The perforations occurring during LTABA highlight the limitations of angiography-guided recanalization and emphasize the need for precise three-dimensional guidance as a priority in laser research. Intravascular ultrasound is the most promising option for guidance of the intraluminal catheters by relaying data on transmural thickness sufficient to steer the probe and to debulk residual atheromatous material.

Acknowledgments

The authors thank George E. Kopchok, biomedical engineer and Director of the Laser Laboratory at Research and Education Institute, Harbor-UCLA Medical Center, for his significant contribution to this study.

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DISCUSSION

DR. JAMES A. DEWEESE (Rochester, New York): As most of you are aware, there has been a frantic rush throughout the country for hospitals to acquire laser equipment. This has been fostered by the showing of the possible usefulness of this modality by a few ingenious pioneers, but its value has been blown out of proportion by the manufacturers and by the media.

Surgeons, radiologists, and even cardiologists have been treating peripheral arterial lesions. Unavoidable turf battles have arisen, and we are fortunate that we do have individuals like Dr. White and his radiology colleagues who are providing a cooperative, aggressive, sane, and honest evaluation of laser technology.

I would like to congratulate them on that.

In evaluating reports of results of laser procedures, it is important to know how the data were obtained. In evaluating the results of 99 reconstructions in Rochester on a more favorable group of patients, we made a very interesting observation.

On this slide you can see that if the results were based on the patient's evaluation of his symptomatic improvement in these patients, 75% of the reconstructions would have been patent at 13 months.

On the basis of hemodynamic measurements only 22% were patent. I would like to compliment Dr. White on his objective evaluation of the results of the procedures performed with both direct examination and periodic hemodynamic measurements.

I do have a question for Dr. White. Where do we go from here? Certainly the 'hot tip' laser is obviously not the answer, and I wish he would expand on his prediction of the future.

DR. WESLEY S. MOORE (Los Angeles, California): This report will join those of others that he cited indicating that not only is "hot tip" laser-assisted balloon angioplasty not a good procedure, it is, in fact, a bad procedure.

When the life table analyses for the conventional femoral-popliteal reconstruction is reviewed, the abscissa, which is measured in years, is compared with the life table analyses for "hot tip" laser-assisted balloon angioplasty, which is measured in weeks and months. It is quite clear where this modality belongs in the therapeutic armamentarium.

The real tragedy is that this procedure was prematurely approved by the FDA. It is being indiscriminately used throughout practice communities and many hospitals are rushing to buy these items of equipment at about a quarter of a million dollars a copy.

I think that this genie can and should be put back into the bottle. We need to put laser back into perspective. Laser is an important area of investigation needing close monitoring of controlled clinical trials. It is by no means a procedure that is ready for indiscriminate application and it certainly is not established therapy.

In closing, I wonder if Dr. White would comment on some perceived differences between the failure rate of 'hot tip' laser with that of directed bare fiber laser. Does the 'hot tip,' in fact, induce greater thermal injury, and is that responsible for a higher failure rate than bare laser fiber-assisted balloon angioplasty?

DR. JOHN A. MANNICK (Boston, Massachusetts): I guess the message here, Dr. White, is not everybody in the audience should run out to attend the next laser course. Is that it?

DR. RODNEY WHITE (Closing discussion): Dr. DeWeese, I appreciate your comments, and thank you for your review of the manuscript. The discrepancy between hemodynamic results and symptomatic relief is an important consideration when evaluating the outcome of endovascular operations. In patients who had successful laser-assisted balloon angioplasties, we were rarely able to achieve the hemodynamic improvement that we would get from a bypass.

There are probably two reasons for this discrepancy. One is limited removal of tissue from the artery with current endoluminal methods, while a bypass procedure or endarterectomy provides a much larger lumen and greater flow. The second reason for improved hemodynamics in bypasses is that the reconstruction completely circumvents resistance to flow in the vascular bed, while angioplasty treats relatively short segments of a diseased artery.

Your second question was: Where are we going to from here?

I think that improved guidance systems such as intravascular ultrasound and/or angiography are mandatory if acceptable recanalization and patency rates are to be achieved. To treat occlusive arterial lesions, the idealized delivery catheter will require three components. The first is a guidance method that will eliminate the primary mechanisms of failure of current angioplasty devices, that is, vessel wall perforation and inadequate removal of lesions. Intravascular ultrasound is the most promising technology in this category by enabling concentric initial recanalization of obstructing lesions. The second component of an ideal system will most likely be by a laser fiberoptic providing miniaturized, precise ablation of tissue. The initial concentric channel established by the laser can then be enlarged by a variety of properly guided devices.

Third, an ideal angioplasty delivery catheter will have a deflectable tip to maintain the ablation components in a concentric luminal position.

Dr. Moore, I agree with your comments. There are now several reports in the surgical literature that substantiate the limited utility of current devices in patients who have conventional criterion for intervention. In the future, carefully controlled clinical follow-up by vascular surgical investigators is required to provide an experienced perspective regarding utility.

You had asked about the difference in failure rates between thermal devices, such as the hot tip, and angioplasty devices using free laser light. At present, we are only performing limited size recanalizations using either type of device, so that long-term patency is comparable. The laser hot-tips do not represent the potential that is being developed using free laser energy systems, but merely use lasers as an expensive method to heat a metal-tip. As demonstrated in this and comparable studies, thermal devices appear to have a limited role in therapy.

In contrast to purely thermal devices, free laser light systems have the potential to make precise, concentric luminal recanalizations via miniaturized fiberoptic delivery. If the free light devices can be developed to perform an endoluminal endarterectomy obtaining a 2- to 5-year patency, as is reported for open surgical endarterectomy of comparable lesions, then repeated recanalizations by a percutaneous or minimal operative exposure in patients who do restenose may be justified. As you know, the free laser-energy systems are becoming readily available. Optimistically, laser angioplasty is entering a second phase of development with improved performance using precisely guided fiberoptic systems.

Dr. Mannick, I think your comments regarding training issues and symposiums are appropriate. I would like to suggest that this money be contributed to the American Surgical Research Fund, and could then be used to support grants designed to address the problems highlighted in this discussion.

Evaluation of APACHE II for Cost Containment and Quality Assurance

JOSEPH M. CIVETTA, M.D., JUDITH A. HUDSON-CIVETTA, M.S.N., and LOREN D. NELSON, M.D.

APACHE II (an acronym formed from acute physiology score and chronic health evaluation) has been proposed to limit intensive care unit (ICU) admissions ('cost containment') and to judge outcome ('quality assurance') of surgical patients. To judge its performance, a 6-month study of 372 surgical ICU patients was performed. When patients were divided by mean duration of stay, mortality rates rose from 1% (short stay) to 19% (long stay) ($p < 0.001$) for patients with APACHE II scores less than 10, but decreased from 94% (short stay) to 60% (long stay) ($p < 0.01$) for patients with APACHE II scores more than 24. Exclusion of patients by high or low APACHE scores would 'save' 6% of ICU days but risk increasing morbidity, hospital costs, and deaths. Grouped APACHE II scores did not correlate with total hospital charges ($r = 0.05$, $p = 0.89$) or ICU days used ($r = 0.42$, $p = 0.17$). Grouping by APACHE II score and duration of ICU stay showed neither symmetry nor uniformity of mortality rates. Surgical patients would not be well served by APACHE II for quality assurance or cost containment.

IN THE 1970S AND 1980S, prediction of outcome and quantitation of the severity of illness were important goals¹⁻⁵ of the emerging discipline of critical care medicine. Although these areas were previously considered in the realm of clinical judgment, the 20th century interest in precision and the voluminous quantities of data generated in intensive care units (ICUs) stimulated the use of a variety of statistical methods to try to attain these goals. In addition to life-and-death predictions and quantitation of the severity of illness, other objectives common to all investigators included evaluation of the performance of individual units relative to a national standard, assurance of the commensurate severity of illness in patients entered into randomized prospective studies, and inter-unit comparisons. However no index has yet achieved the goals set out by their developers. In 1983 the National Institutes of Health Consensus Development Conference on Critical Care Medicine⁶ reviewed data presented by the authors of these different indices and concluded:

The combination of life-threatening diseases, finite resources, invasive therapeutic and monitoring techniques, and high costs makes the need for adequate data on which to base decisions a high priority.

From the Division of Surgical Intensive Care, the Department of Surgery, University of Miami School of Medicine, Miami, Florida

Such research is aimed at determining how ICUs can be used for the maximum benefit of the ICU population. This research should include procedures for "triaging" patients so that admission is not denied to patients who can most benefit from an ICU as well as excluding patients who have no reasonable chance to benefit from treatment. Research aimed at developing accurate outcome predictors as a function of initial presenting condition, diagnoses, and other on-going prognostic variables should be encouraged.

There are many reasons for the failure of the predictive indices. Despite the acknowledged inaccuracy in predictions and their well-perceived theoretical and practical bases, more recently there have been substantial efforts to apply these unsatisfactory predictive indices to cost containment and quality assurance. Initially acute physiology scores were hypothesized to be useful in identifying 'low-risk monitor' patients within a medical/surgical ICU.⁷ The supposition was that patients who had less than a 10% chance of requiring a 'specific ICU type' intervention need not be admitted. This hypothesis was then transformed into a principle to limit ICU admissions in a retrospective study performed by the Government Accounting Office titled 'Past Overuse of Intensive Care Services.'⁸

Cost containment would also be fostered by excluding patients with a 100% likelihood of dying. In these cases, no current form of therapy would be successful and all resources so expended could be considered wasted. A national validation study of APACHE II, a termed derived from the original acute physiology score and chronic health evaluation, discovered significant differences in outcome in different ICUs.⁹ The authors then hypothesized that these differences were due to organizational differences; thus the index was used as a quality assurance tool.

More recently a further evolution of the acute physiology score, APACHE III, has been proposed.¹⁰ The current plan is to provide an automated version, 'so simple and routine that the majority of this nation's adult ICU admissions are entered automatically into the system and updated scores are calculated each day.'¹¹ The intended

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goal would be to provide comparisons of individual unit performance with national norms to purchasers (hospitals, insurers, and payors).

Because there are general limitations of scoring systems and specific problems with respect to quantifying the severity of illness in surgical patients, we elected to study a surgical ICU to determine if APACHE II could describe the population in a uniform manner, that is, a given score should have similar expression in terms of mortality and if APACHE II could pinpoint patients for exclusion from ICU admission, which would result in real and significant resource savings without jeopardizing patient safety.

Materials and Methods

Patients admitted to the Surgical Intensive Care Unit of the University of Miami/Jackson Memorial Medical Center were entered during a 6-month study period. Duration of ICU stay, outcome, total hospital charges, and the variables to calculate APACHE II scores were collected by a single trained observer (JHC). In addition to admission APACHE II scores, calculations were repeated on days 2, 3, 5, 7, 14, and 1 day before the patients' discharge from the ICU. APACHE II score is comprised of three components: age, chronic health evaluation, and acute physiology score. Points for age vary from 0 (age less than 45 years) to 6 (age more than 75 years). For surgical patients, the presence of severe organ system insufficiency adds 5 points if the patient had emergency surgery and two points if the surgery was elective. The acute physiology score consists of 11 variables assigned from 0 to 4 points, depending on a defined degree of abnormality. The weights for each variable were initially set by a panel of experts and subsequently modified empirically and by

PATIENTS WITH SAME INITIAL APACHE 2 DIVIDED INTO ABOVE AND BELOW MEAN STAY

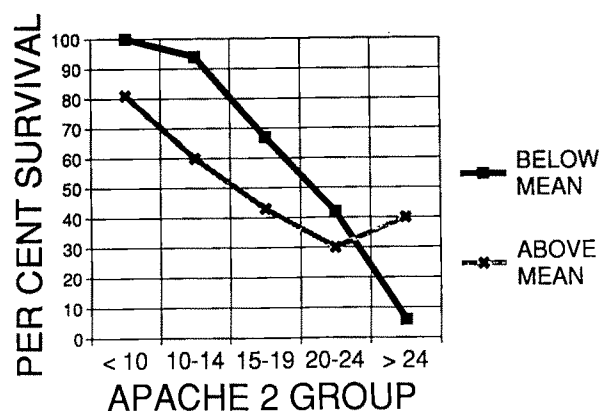


FIG. 2. Patients were subdivided into five groups according to their admission APACHE II scores. For APACHE II groups < 10 and 10-14, there was a statistically significant increase in mortality rate with increased duration of ICU stay. Conversely, for patients whose APACHE II scores were more than 24, the mortality rate was significantly higher if the duration of ICU stay was more than 5 days. Thus there were opposite and statistically significant differences in mortality rates for the patients with the highest and lowest APACHE scores, depending on the duration of ICU stay.

statistical analyses.¹² The actual Glasgow Coma Score is subtracted from 15 to give the 12th component of the acute physiology score.

Data were analyzed by t test, chi square analyses, and analysis of variance (ANOVA) using commercially available statistical packages for DEC (Digital Equipment Corp., Maynard, MA) and Macintosh (Apple Computer, Inc., Cupertino, CA) microcomputer systems. Results were considered statistically significant if $p < 0.05$.

Results

A total of 372 patients were entered into the study. Of these, 292 (78%) survived to hospital discharge. Mean APACHE II score of survivors was 9.5. The other 80 patients (22%) died. Mean APACHE II score on admission for those who died was 19.7 ($p < 0.05$ compared to survivors). The total number of bed days used was 1644; the mean length of stay was 4.5 days. To determine if the duration of ICU admission affected mortality, patients were divided into two groups based on length of stay: 4 days or less (less than mean stay) or 5 days or more (exceeding mean stay). In the group less than mean stay, 36 patients (13.1%) died and 238 patients (86.9%) lived. In the patients exceeding mean stay, 59 patients (59.6%) died and 40 patients (40.4%) lived. This difference was significant (chi square = 44.7; $p < 0.001$) (Fig. 1). Mortality rates for patients exceeding and less than mean stay were compared according to their initial APACHE II scores (Fig. 2). There was a statistically significant decrease in survival associated with increased duration of ICU stay

DURATION RELATED MORTALITY

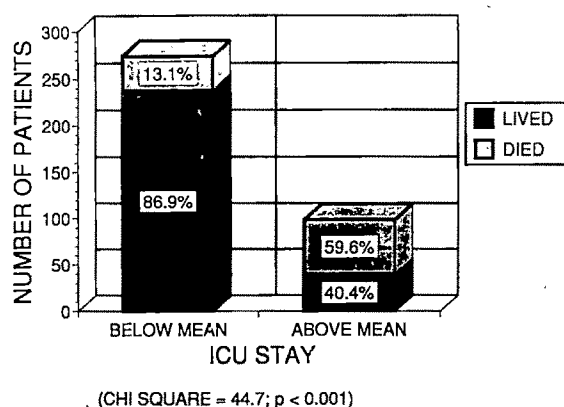


FIG. 1. Mean duration of stay in this study was 4.5 days. Patients were divided into durations of 4 days and less or 5 days and longer. Mortality rates were then computed and compared by chi square analysis. There is a statistically significant increase in mortality rate in patients whose duration of stay was longer than the mean of 4.5 days.

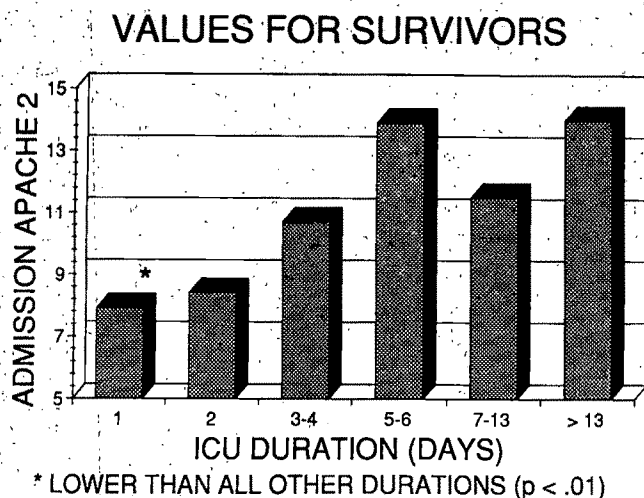


FIG. 3. APACHE II admission scores calculated for surviving patients divided into groups based on the duration of ICU stay. Patients who stayed for 1 day had the lowest mean score, although there was considerable overlap in terms of individual patient scores, and the ultimate ICU duration could not be predicted.

for patients with initial APACHE II score less than 10 (chi square = 12.43, $p < 0.001$) and 10 to 14 (chi square = 13.20; $p < 0.001$). However for those patients with an APACHE score more than 24 on admission, there was a significant increase in of survival with an increased duration of ICU stay (40% versus 6%; chi square = 7.38, $p < 0.01$).

Patients might be considered for exclusion from ICU admission if low APACHE II scores were correlated with survival and short ICU duration. Admission APACHE II score was significantly lower for surviving patients who had a 1-day admission when compared to all other durations (Fig. 3). Exclusion of patients with high scores

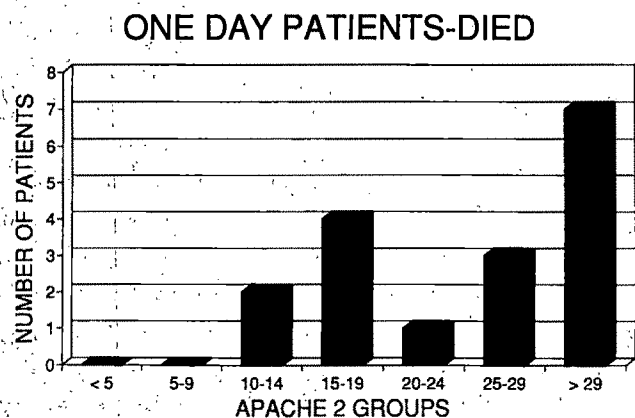


FIG. 4. Distribution of the patients who died on their first ICU day with respect to initial APACHE II score. While 7 of the 17 patients had APACHE II scores more than 29, the other 10 patients were distributed among the groups 10-14, 15-19, 20-24, and 25-29. Thus patients with relatively low APACHE II scores died on the first ICU day, despite the fact that their measured degree of physiologic abnormality by APACHE II score was not high.

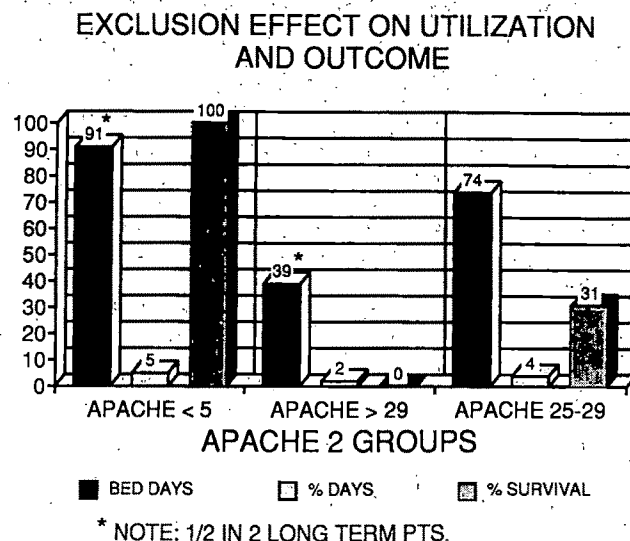


FIG. 5. Patients in three subgroupings were considered in terms of the overall effect of exclusion from the ICU on bed-day use and survival according to APACHE II group. For patients with an APACHE II score less than 5, 100% survived with ICU care, but only 91 bed days would have been saved. Approximately one half of these days were used in caring for two patients with initial APACHE II scores of less than 5 who still required weeks of ICU care before they could be discharged. At the other end of the spectrum, patients with APACHE II scores more than 29 used 39 bed days. All of these patients died. This would have saved approximately 2% of the total bed days. However, one half of these days were used in long-term patients as well. In an attempt to increase the savings in bed days, the patients with APACHE II scores of 25-29 were analyzed. Seventy-four bed days would have been saved; however there was a 31% survival rate. It is very likely that, should all of these patients have been excluded, they would not have survived.

might be recommended because of the futility of care. All dying patients who had a single-day admission were then analyzed by APACHE II group on admission (Fig. 4). While 7 of 17 patients had an APACHE score more than 29, ten patients who died on the first ICU day had APACHE scores of less than 29.

If all patients with an initial APACHE score less than 5 had been excluded, 91 (5%) of the total 1644 bed days might have been 'saved' (Fig. 5). Approximately one half of these days were used in the care of two patients. Excluding patients with APACHE II scores more than 29 would have saved 39 (2%) of the bed days. Again one half of these days were expended for two patients. In an attempt to improve potential savings by exclusion, patients with an APACHE value of 25 to 29 were analyzed. Seventy-four days (4%) were used to care for these patients but 31% survived after ICU care.

If the severity of illness spectrum is defined by duration of ICU stay and APACHE II score, then there should be a steady progression from the lowest score in a surviving patient with a 1-day stay, mid-range scores for surviving and dying patients with the longest ICU stay and, finally, the highest scores should occur in the patients who died

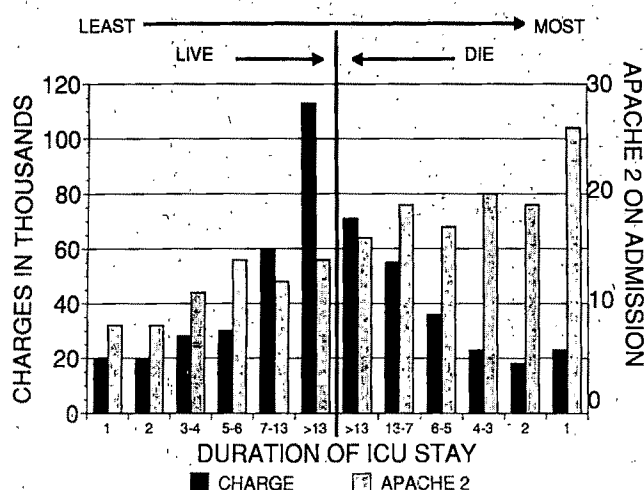


FIG. 6. A severity of illness spectrum was created on the premise that patients who stayed in the unit for 1 day and survived were the least sick, while patients who died during their first ICU day were the sickest. This spectrum based on the duration of ICU stay would increase to a midway point for patients who stayed for more than 2 weeks and lived with the next sickest group, representing those patients who stayed for more than 2 weeks and died. APACHE II scores show a pattern of generally increasing values from the least to the most sick. However total hospital charges (in thousands of dollars) bear no relationship to the APACHE II score. Thus increasing severity of illness is not accompanied by increasing charges. In fact the patients with the highest APACHE score (1-day patients who died) had identical hospital bills to the patients with the lowest APACHE score (1-day patients who lived).

during their first ICU day. The progression of grouped APACHE II scores using this concept of severity of illness is compared to resource use as described by mean hospital

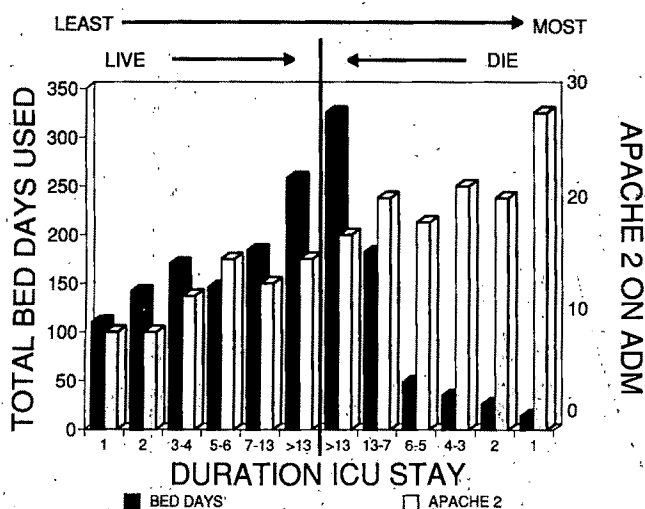


FIG. 7. The severity of illness spectrum was again based on the premise that the least sick patient spent 1 day in the ICU and lived and the sickest patient spent 1 day in the ICU and died. Total use of bed days is graphically represented by the dark stippled column, whereas APACHE II score is represented by the light stippled column. There is no overall correlation, and, in fact, patients with the highest APACHE scores seen on the right portion of the bar graph used the least bed days. There would be little savings from their exclusion.

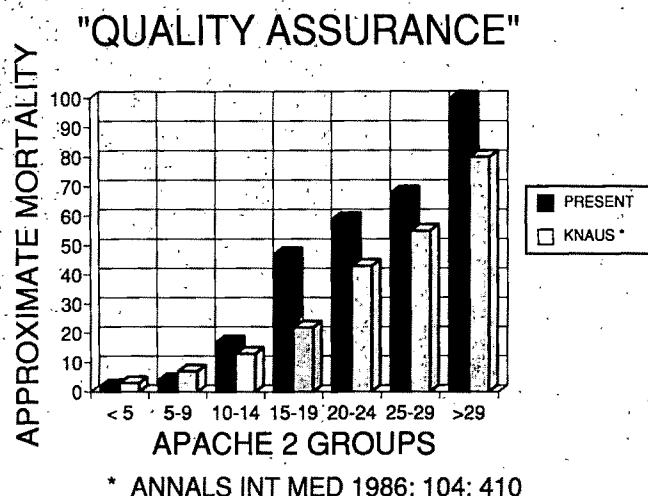


FIG. 8. Comparison of mortality rates for given APACHE II groups in the present study and a 13-hospital national study reported by Knaus.⁹ Note that at the four higher APACHE II groupings, mortality rate in the present study was approximately 20% higher. One immediate inference might be that the quality of care rendered in the present study was inferior to the national standard because the observed mortality rate exceeded that calculated from the national data base. However additional factors must be considered for populations comprised of elective surgical patients and trauma patients in a community with a well-developed urban emergency medical system.

charges (Fig. 6) and total ICU bed days used in caring for patients in each category (Fig. 7). There is no significant correlation between APACHE II score and total hospital charges ($r = 0.05$, $p = 0.89$) nor between APACHE II scores and total ICU bed days used ($r = 0.42$, $p = 0.17$).

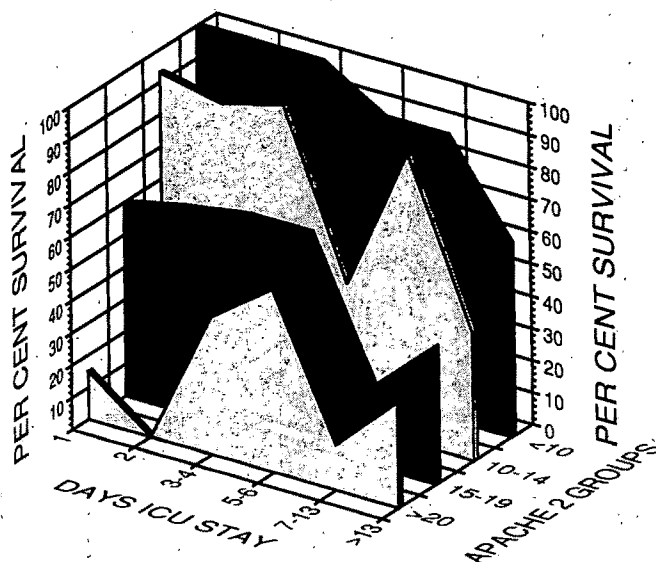


FIG. 9. Three-dimensional representation of survival rates as a function of both APACHE II score and duration of ICU stay. For any given APACHE II group, there are markedly different mortality rates, depending on duration of stay. Neither symmetry nor uniformity on any axis is present. Therefore factors other than admission APACHE II scores must affect mortality rates and these factors would not be evaluated if APACHE II alone were used as an assessment tool.

Approximate mortality rates for patients in the present study were matched to rates for patients reported in 13 hospitals in a national study.⁹ Mortality rates for the four subgroupings of APACHE II scores more than 15 were approximately 20% higher in this study (Fig. 8).

Survival rates were then calculated for patients on the basis of both admission APACHE II score and duration of ICU stay (Fig. 9). In each APACHE subgroup, survival rate varied according to the duration of ICU stay or, stated another way, patients with the same APACHE II score but different ICU stays had different survival rates.

Discussion

All scoring systems can be considered to contain certain general limitations as well as those specific to the previous effects of therapy seen in surgical patients. Certain limitations can be seen intuitively. An unpredictable and unique event is often the only determinant of outcome. Idiosyncratic reaction to a drug or a massive fatal pulmonary embolus in an individual patient 1 month after ICU discharge cannot be predicted.

If a factor ultimately affecting outcome is not included in the calculation of the index, its effect cannot be predicted. The 'sepsis syndrome,' so often the cause of death in surgical patients, is difficult to define and is not addressed directly by APACHE II components. Furthermore multiple-organ system dysfunction is prevalent in the surgical patients who use the most ICU resources. If the organ system is functioning normally on admission and is so measured by the included variables, the ultimate effect of later dysfunction cannot be predicted.

In addition, because prediction is an imperfect science, most authors discuss the false-classification rate, which approximates 10% to 15% for all predictive indices.¹³ Practically speaking, the known false-classification rates will be expressed in ways that are detrimental to present standards of care. One type of false classification is that patients who are expected to live may die, even with ICU care. In fact the policy of the exclusion of 'low-risk monitor' patients does not address the issue of later development of significant complications. The Consensus Development Conference⁶ discussed the potential for the development of complications in excluded patients citing that, if these patients were to be excluded safely, care in routine care areas should be no less effective than care in the ICU. In today's hospitals, because ICUs cluster the sickest patients and because skilled nursing care is limited both within and outside the ICU, this premise often is not justified. If unexpected deterioration of the ICU-excluded patient occurs in a hospital care area without specialized equipment and trained, experienced physicians and nurses to respond rapidly and effectively, a return to the unsatisfactory pre-ICU standard of care can be pre-

dicted. The increase in mortality rates with long-term ICU admissions seen in Figure 2 and the lack of consistent correlation of survival, low-admission APACHE score, and short ICU duration of care all suggest that this exclusion of patients based on low APACHE scores would not be safe. In fact this policy would recreate identical conditions to those that led to the development of surgical ICUs more than 20 years ago.

The second expression of a false-classification rate is that patients who are predicted to die actually live with ICU care. This is substantiated by the fact that patients with a high initial APACHE score have a higher survival rate with increased duration of ICU stay (Fig. 2). However if this care is not provided immediately (patients are excluded as too sick), it seems very likely that an early death will result. In terms of the actual number of patient days and percentage of total ICU days expended, little savings can be expected (Figs. 5 and 7). The recent suggestion¹⁴ that the excluded patient can be given 'comfort care' seems unrealistic because patients with this degree of physiologic abnormality usually die within minutes to hours after treatment is terminated, whereas the concept of providing aggressive comfort measures¹⁵ usually is applied to terminally ill patients who can make their wishes known and who have days to weeks of life remaining. They bear little resemblance to the ICU patient with an initial APACHE score more than 29. The increased survival rate associated with a longer duration of ICU stay suggests that the resolution of even a severe degree of physiologic abnormality is only possible if patients are given continued care; if ICU admission is denied, it seems likely that these patients will die.

In addition to these general limitations, there are specific considerations with respect to surgical patients. The original APACHE system⁵ was intended to assess the patient independent of therapy. While this may be relevant to medical patients who may present to the ICU without previous therapy, APACHE scores in surgical patients may be artifactually raised or lowered, depending on therapeutic objectives and the length of pre-ICU care. Unfortunately, for surgical patients, there is another aspect that has not been addressed, even in the proposed revision called APACHE III,¹⁶ which will include pre-ICU data. While the inclusion of pre-ICU data initially might be considered to correct for the effects of previous therapy, in elective surgical patients who comprised 50% of the study group, one might view the anesthesiologists's physiologic objective as maintaining the lowest possible APACHE score by anticipating and preventing abnormalities so that no acute physiology points are accrued. For instance, if a complicated intestinal operation required 8 hours, many blood transfusions, fluid and drug administration, and yet, as a result of the constant attention, there were no changes in mean arterial pressure, arterial

pH, or hematocrit, it is clear that the patient has undergone a significant physiologic stress that would not be measured by these components of APACHE II. If preventive care had been less expert, the same blood loss and surgical stress might have led to hypotension, acute anemia, and even metabolic acidosis. The patient's APACHE score would then be higher. While there is no immediate answer to providing an accurate assessment of this challenge, this masking of physiologic abnormalities may explain our 'excessive' mortality rates. Well cared for patients will be penalized because they have not accumulated enough points from physiologic abnormalities to qualify for ICU admission. They will be relegated to lesser care facilities, which will be viewed as appropriate yet less expensive for the measured degree of their 'noncritical' illness. This premise can only be disproved by the development of serious complications that lead to markedly increased costs, longer subsequent ICU stays for developed complications, and preventable deaths. Ten years ago, Zook and Moore¹⁷ recognized that the opposite was true and stated that 'considerable cost saving and reduction in human suffering would be possible if the frequency of adverse events could be reduced, even by a small percentage.' Thus the potential for increased costs and suffering appears to be greater than any possible savings that might result from a policy of exclusion on the basis of low APACHE II scores.

With respect to artifacts in APACHE II scores, the opposite may also occur: the use of intentional hypotension, hypothermia, muscle paralysis, and mechanical ventilation may result in a high APACHE score, supposedly measuring severe physiologic abnormalities, yet be associated with a very low mortality rate. Patients who have undergone cardiac surgery¹² have been excluded from APACHE II analysis perhaps because the effect of these often-selected therapeutic interventions render incorrect mortality predictions. Patients who suffer trauma in urban areas with well-developed emergency medical systems,

which have short response times, may never develop abnormalities in APACHE II components due to the rapid initiation of therapeutic support. The extent that this counteracts and obviates effects that would have occurred had treatment been unavailable is immeasurable but has not been considered in subsequent refinements planned for APACHE III.¹⁴

The exclusion of the 'low-risk monitor' surgical patient must be considered from the standpoint of factors other than physiologic abnormality. The initial suggestion⁷ made after the identification of these patients was to decrease the ICU stay from 2 days to 1 day. Subsequently, however, the Government Accounting Office⁸ and articles by the authors of the original study¹⁸ suggest preventing admission to the ICU. This conclusion is said to be supported by a study¹⁹ in which a limitation of ICU beds resulted in restricting the admission of 'low-risk monitor' medical patients without increased morbidity and mortality. In most hospitals today, both admission and duration of ICU stay are carefully scrutinized and further exclusionary tactics, particularly in surgical patients, must be followed by an increase in morbidity, hospital costs, and mortality. In this study 110 elective surgical patients were discharged after 1 day of ICU care. The admission APACHE II scores in these patients were significantly lower than in survivors with other durations of ICU care (Fig. 3), but the ultimate duration of ICU stay was not obvious to clinicians at the time of admission. However other patients, who also had an APACHE II score less than 10, did not fare as well. There was a 20% mortality rate if the ICU stay was 5 days or longer (Fig. 2).

Given the scarcity of available ICU beds in our own ICU, we have been using a clinical triage system, attempting to add to the validity of ICU-exclusion decision by incorporating additional opinions and additional data into the decision-making process.²⁰ In our hospital only 5% of elective surgical patients were considered by their surgeons for postoperative intensive care. If, at the end of the op-

TABLE 1. *Effect of Current Clinical Triage*

Type of Patient	Percentage Consults	Percentage Mortality	ICU Days Used	Hospital Days	Charges (\$ × 1000)
Preop ADM	13	12	5 ± 7	14 ± 11	28 ± 21
OR PA CATH	10	15	5 ± 6	17 ± 14	37 ± 25
ICU only	49	4	1.5 ± 1	15 ± 18	24 ± 26
RR postop	29	2	0	10 ± 13	16 ± 22

Distribution and outcome of elective surgical patients considered for ICU care. Preop ADM = patients admitted to the ICU 1 day prior to surgery for invasive hemodynamic monitoring; OR PA CATH = patients selected for intraoperative monitoring by the anesthesiologist; ICU ONLY = patients who never required invasive monitoring but were given intensive nursing or monitoring in the ICU after operation; RR postop = patients judged by surgeon and anesthesiologist not to need the postoperative ICU care originally requested; CHARGES = total hospital

charges in thousands of dollars. ICU consult patients represent 5% of total elective cases. Twenty-nine per cent were deemed stable at the end of the operation and "triaged" to the recovery room. Though the mortality rate was significantly lower than the rates observed in the groups admitted to the ICU, the elimination of the ICU admission did not result in a statistically significant decrease in either total hospital days or total hospital charges. (Data adapted from Civetta²⁰)

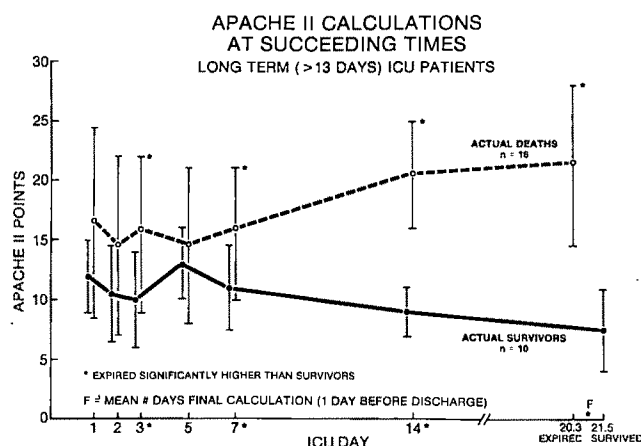


FIG. 10. The 26 long-term patients (more than 13-day duration of stay) were divided into the patients who actually lived or died. APACHE II calculations were made on admission, at days 2, 3, 5, 7, 14, and the day before the patient was discharged from the unit or died. The final calculation was performed approximately 3 weeks after hospital admission in both cases (20.3 days in patients who died and 21.5 days in patients who survived). Data points are displayed as mean $\pm$ standard deviation. Overlapping ranges occur until the calculation performed on day 14. The mean values became statistically separable on day 3 but were indistinguishable on day 5. On day 7 values were again statistically significant and remained so. (Reprinted with permission from Civetta J., *The Clinical Limitations of ICU Scoring Systems. In Problems in Critical Care* 1989; 3:689.)

eration, in the opinion of the surgeon and anesthesiologist, the patient is considered stable, to have tolerated the procedure well, and to be at low risk for developing problems requiring ICU care, the patient is transferred to the recovery room. Twenty-nine per cent of the patients satisfy these criteria. Mortality rate in this group of patients was significantly lower than in patients actually admitted to the ICU. However, by statistical analysis (ANOVA), there were no differences and, thus, no savings in terms of total hospital charges or total hospital days (Table 1).

There have been no randomized prospective studies concerning the effect of exclusion of patients; however a number of factors has led to a chronic shortage of ICU beds for elective surgical patients at our hospital. This affects non-ICU surgical patients as well. Patients remain in the recovery room to receive needed care; because these patients require more care than standard recovery room patients, the recovery room census must be curtailed, which results in back-up of the operating rooms and cancellation of surgery for other non-ICU patients. Other areas have been set aside for these 'low-risk monitor' patients who still need care in excess of that available in routine care areas. The cost to the hospital and the charges to the patient to create these intermediate care areas are essentially the same as to provide care in the ICU. Thus exclusion appears to have no benefit in terms of hospital functioning, especially because the concentration of physicians, nurses, and equipment to care for the patient

needing more than routine floor care (the rationale for creation of the ICU) now must be abandoned.

A second specific surgical consideration is that the severity of physiologic abnormality, as judged by APACHE II, does not appear to be an appropriate measure of resource utilization. Hospital charges are not correlated with APACHE II scores. Indeed the patients who die within 1 day and have the highest APACHE scores have identical hospital bills to survivors given 1 day of ICU care who have the lowest APACHE scores and are at the opposite end of the spectrum (Fig. 6). Furthermore the crucial measure of utilization, total ICU bed days provided, again bears no relationship to APACHE scores (Fig. 7). In fact 35% of the total bed days were provided for just 7% of the patients who remained in the ICU for more than 2 weeks. Forty-four per cent of these patients survived, which can be considered justification for the efforts expended and resources allocated.²¹ These patients have previously been analyzed in greater detail.²² APACHE

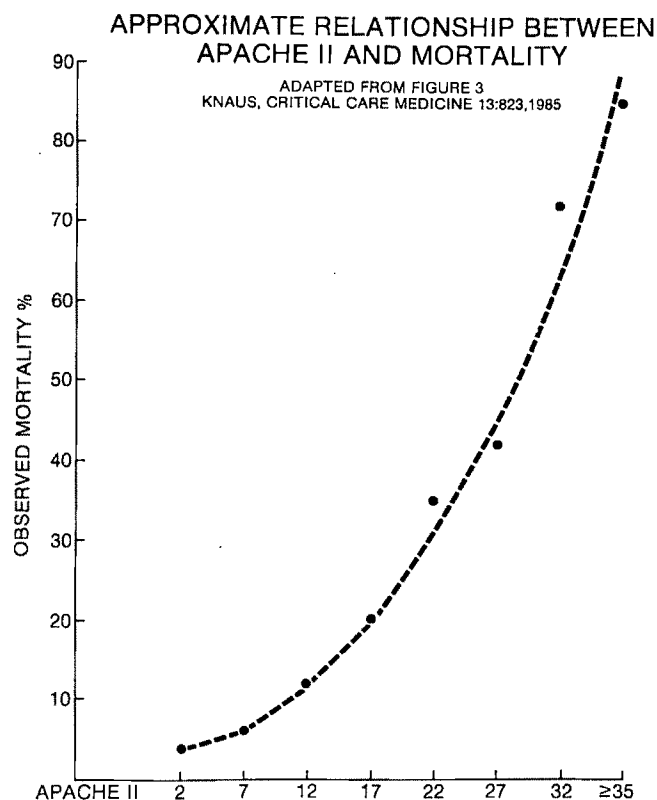


FIG. 11. The approximate relationship between APACHE II score and mortality rate for surgical patients is delineated as a curve adapted from the bar graphs seen in the original article. It is clear that increasing APACHE II scores are associated with an increasing observed mortality rate. However the patient, with mid-range scores who have mid-range mortality, represented only 7% of our ICU population and little insight is gained into a description of these patients by learning that their APACHE II scores are "in the middle" and that mortality rate hovers around the "cut point" used in prediction. (Reprinted with permission from Civetta J., *The Clinical Limitations of ICU Scoring Systems. In Problems in Critical Care* 1989; 3:690.)

scores overlap, are not separable by statistical analysis on admission, and fall into the mid-range throughout the patients' ICU stay (Fig. 10). In addition, if these APACHE scores are considered in relationship to reported mortality rates¹² as displayed in Figure 11, it is clear that APACHE II does not assess the risk of mortality in the subgroup of patients, all of whom died after more than 2 weeks of ICU care. Expected mortality rate for the admission APACHE score was approximately 20% and rose to just 35% for the APACHE score calculated on the day immediately preceding the patients' actual death (Fig. 12).

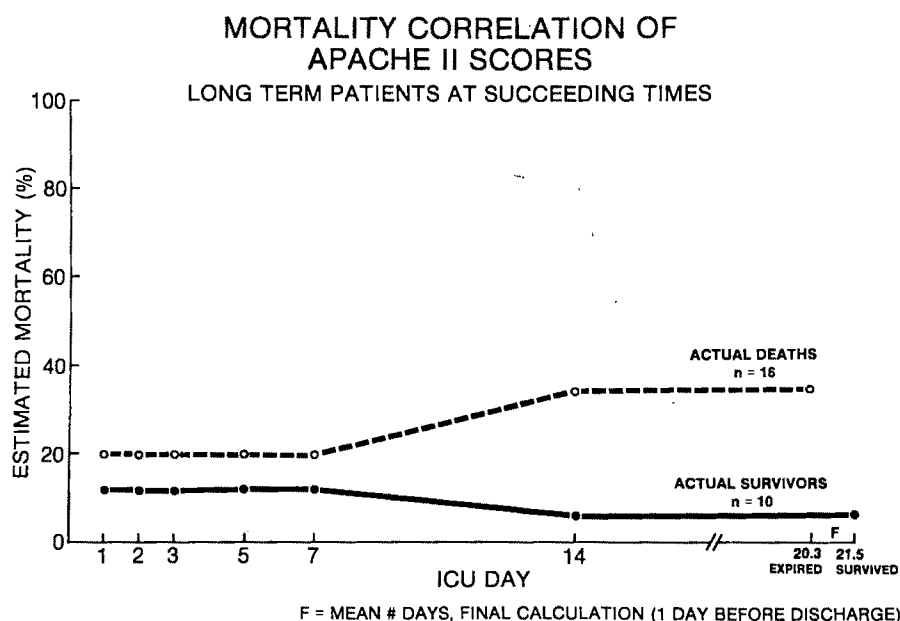
From a quality assurance standpoint, if individual unit mortality rates were higher than overall rates in the national data base, unit performance could be judged as inferior (Fig. 8). The difference in mortality rates will also occur if the patient mix is different (such as a higher percentage of the long duration patients shown in Figure 2) or when intentional artifacts of preventive care falsely lower the APACHE score in surgical patients. Even the refinements in APACHE III do not seem capable of distinguishing artifact from inferior performance. It is important to remember that this is not just a question of scientific validity because interpretations are already made by the government and the public often incorrectly based on presently available overall hospital mortality rate information.²³ The unfortunate implication that hospitals with high mortality rates deliver poor quality of care has been made in many newspaper articles after the release of this information. Higher observed mortality rates, whenever due to specific problems inherent in determining the severity of illness in carefully attended patients

during surgery, will then create extensive and unnecessary review to determine if performance was inferior. The increased time, effort, and expense used for these nonmedical functions must unavoidably increase the costs and decrease the efficiency of dollar resources by reducing the amount of time and number of personnel available to provide true medical care functions. To the extent that this occurs, the application of APACHE to surgical patients will not attain the objectives of quality assurance and cost containment, but rather help to produce the opposite effect.

Any methodology whose purpose is to attain the objectives of cost containment and quality assurance must describe the population in a uniform manner, especially if this description is said to be independent of treatment.⁵ However, when patients are considered from the standpoint of initial APACHE II scores and duration of illness, there is neither symmetry nor uniformity (Fig. 9). The marked difference in survival within an APACHE II group, depending on the duration of ICU stay, indicates that therapy must have an effect and that there are important other variables affecting outcome.

For all these general and specific limitations in surgical patients, exclusion of patients on the basis of APACHE II scores would not result in significant savings. In addition exclusion would create risks of increased morbidity, mortality, and costs. In fact this policy would re-establish the conditions that led to the development of the surgical ICU. Because of the lack of uniform expression of APACHE II scores, even in a single unit at the same time, APACHE II would not appear to assess quality of care in

FIG. 12. APACHE score for surgical patients correlated with mortality observed by Knaus in an article published in *Critical Care Medicine* (1985; 13:823). The APACHE values calculated for these long-term patients (ICU stay more than 13 days) were used to derive an expected mortality rate from the relationship seen in Figure 11. Estimated mortality rates are reported for the group of patients who lived and those who died. On admission the 16 patients, all of whom died, were predicted to have a 20% mortality rate. From the APACHE II score calculated on the day before their actual death (F or final value), survival rate was estimated to be only 35%. Finally the curves for survivors and patients who died were parallel and at low estimated mortality for the first 7 days. (Reprinted with permission from Civetta J., *The clinical limitations of ICU scoring systems. Problems in Critical Care* 1989; 3:689.)



surgical patients. Despite the tremendous mass of data that has been analyzed and the changes proposed for APACHE III, it does not appear that surgical patients would be well served by the application of this or a similar methodology for the purposes of quality assurance, cost containment, measurement of severity of illness, or prediction of outcome.

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DISCUSSION

DR. ROBERT H. DEMLING (Boston, Massachusetts): I would like to put the importance of this paper into perspective. The two most nationally prominent severity scoring systems now being used in ICUs in this country, namely, APACHE and MEDA System, were designed for medical patients and never validated for surgical patients. A number of state governments have mandated their use as the principal and sole evaluation tool for all patients, surgical and medical, to measure appropriate ICU utilization and to assess outcome. These data will then be used for hospital mortality ranking and for payment purposes.

The Federal Government, especially HCFA, is posturing itself in a similar manner. That is, one system for all types of patients.

Dr. Civetta has demonstrated to us that APACHE does not work in surgical ICU patients to monitor appropriate resource allocation and quality assurance.

Recent data generated by the American College of Surgeons Task Force on Surgical Critical Care, of which Joe is a member, has also obtained data to verify that APACHE does not work to predict multi-system organ failure in surgical ICU patients or to predict surgical ICU mortality rates, especially in trauma patients, where positive fluid balance is equally as sensitive as APACHE II. These last studies are in press in several surgical journals at present.

Dr. Civetta's data can now be used by all of us to help avoid further inappropriate mandates using APACHE, and MEDIS system, which is a variant of APACHE, that is, a physiologic scoring system.

The difficulty is that surgeons are the last people to be aware of the fact that a system has now been initiated in their hospital on which they

will be judged, even though the system is inappropriate. In many parts of the country now, APACHE or MEDIS is before the state legislatures as a potential mandate for all patients.

Dr. Civetta has, by his presentation, increased our awareness of this problem and gives us some ammunition at this time to help us eliminate this freight train of legislation, which is inappropriate.

In discussing this topic, however, an obvious question comes to mind. We need some form of assessment tool in intensive care units to determine resource utilization and quality assurance. Until a surgical ICU tool is developed that is appropriate, I would like to ask Dr. Civetta what he thinks would be an appropriate current tool for JCAH purposes. Should this tool be uniform for all surgical patients throughout the country or should each individual ICU director according to his area develop his own individual system?

DR. WILLIAM R. DRUCKER (Bethesda, Maryland): Dr. Civetta has been interested in intensive care for a long time, and part of that interest has been devoted to the problem of rising costs. The ICU today consumes about 15 to 20% of any hospital budget. It is estimated that about 1% of the gross national product is spent on the ICU. Thus, it is clear that efforts need to be directed to bring these costs under control.

We, as physicians, are concerned that the DRGs properly reimburse for our care of the injured patient because they do not take into account the case mix and the severity of illness. So we need an estimate of severity of illness for this and other reasons.

The development of the APACHE score is just one of at least seven or eight different methods that have come forward, as Dr. Demling just

mentioned. APACHE is widely used across this country, and Professor Robert Shields, who is sitting in the back, says they are now using it in England.

There are several hypothetical concerns about this method worth identifying that we, as surgeons, need to know.

First of all, this method takes cohort groups to derive coefficients for a logistic function. Then this is used to predict outcome (probability of survival). The problem is that those groups are too heterogeneous to be used to make valid predictions. The second concern is that the groups were quite small, at least the ones that were used to derive APACHE II. And it looks like an APACHE III is not going to improve on that very much. The groups are much too small for derivation of this important factor.

Third, the groups do not include an anatomic description. The groups are all based on physiologic variation, but there is quite a difference between an injury to a bone and an injury to the central nervous system. That leads to the fourth concern, that is, the same APACHE score can be derived from injuries to different constellations of organs. For instance, a head injury may be given the same score as an injury to another anatomic area that has a very different prognosis for recovery in terms of both morbidity and mortality.

Finally, the APACHE methodology does not take into account therapy. Many patients, before they get to the ICU where the APACHE score is first applied, or even in the emergency department, receive prior therapy. Therapy can be deceptive. It can either raise or lower APACHE scores.

In this very careful critical clinic study of the APACHE methodology, Dr. Civetta has demonstrated that these potential concerns are very real when applied to the life situation of the surgical intensive care unit. He justifiably warns us to be careful in the application of a flawed methodology to derive outcome measures and, using the outcome measures, he warns us not to make judgments of quality of care or to derive strategies for the control of costs.

Dr. Civetta, I have one question. I noticed in your manuscript that you measured the APACHE scores on successive days during the patient's course on the intensive care unit. Does this serial study of APACHE scores provide a better means to predict outcome? Is there some usefulness of the APACHE methodology if one applies it on a daily basis in watching your patients?

DR. BEN EISEMAN (Denver, Colorado): The data in this paper, which I was fortunate to review, indicate that APACHE II is not a good method of determining ICU admission. The obvious response is "So what?" My remarks are intended to emphasize to the membership the significance of such findings in both the present and future health care payment environment.

Somewhat belatedly after introducing the DRG payment system for paying hospital bills on the basis of diagnosis, health care payers discovered that severity of illness modulated health care costs: one patient with a myocardial infarct or jaundice was not identical to another with the same diagnosis. They then ordered their staff to find a simple method for measuring severity of illness. They found of course that this is an enormously complicated problem.

There are currently at least five major methods for measuring severity of illness designed to predict appropriate hospital charges. They differ in what they measure, but their objective is the same. Some, such as disease staging, rely on extent of disease similar to the TMN grading of tumors. Others, such as MEDIGROUPS and Computerized Severity Index Systems, heavily weigh co-morbidity factors that have an astonishing correlation with outcome and hospital charges when applied to large samples of patients. Some of these systems have been applied to literally millions of hospitalized patients.

The APACHE tribe of scoring systems are, as most of you know, primarily based on physiologic measurements such as we clinicians rely on for day to day management of very sick patients. They were NOT designed to guide health care economic decisions and therefore it should come as no great surprise that they do not fulfill the requirements of health care payers.

My first point, therefore, is to emphasize to health care payers that severity of illness scores are not all the same. Predictably, a series of scoring systems will be required to answer a clearly defined need, be it the decision to place a patient in an ICU, or cost of hospitalization, or admission to hospital for a chronic illness.

My second point is to emphasize that such severity of illness scores are going to play an ever more important role in establishing guidelines and standards of care and expected outcomes that health payers have already indicated are to be pivotal in guiding decisions for payment. Let there be no mistake, industry, insurers, and government are going to want standards by which they can evaluate what they are buying and what they can rightfully anticipate in the way of results from our patient management. Severity of illness will be one of the most basic factors in such a data base. If a given hospital, or a given clinician, do not measure up to the standards, we will find that the payers will refuse to pay. It takes little imagination that this not only equates to, but actually supersedes, measures such as board certification or qualification. Indeed, it will equate with licensure.

If you grant me the validity of this prediction, then we in leadership roles in surgical care have two options. The first will be the all too frequent one of wringing our hands and ignoring or decrying the trend and allowing others less qualified than ourselves to establish the guidelines and standards. The all too familiar frustrations of a rearguard action will once again be ours.

The other more responsible strategy will be to admit reality and to take a leadership role in creating practice guidelines standards and outcome expectancies for which I believe health care payers will be grateful. Every student of such health policy issues knows that severity of illness scoring systems underly such systems.

This is why this paper by Dr. Civetta is important. It alerts this senior surgical association to the decision that we must make: Should we passively allow others less qualified than ourselves to define severity of illness and standards of practice, or should we step forward and let the payers understand that we are more knowledgeable than any others, that we recognize our societal responsibilities in this matter, and that we are anxious to play a leadership role?

DR. DONALD TRUNKEY (Portland, Oregon): I think Dr. Civetta has really done us a great service if for no other reason than to point out to HCFA that APACHE has not been validated for surgical patients, and therefore, cannot be used in cost-containment issues. In addition I want to strongly emphasize that it cannot be used for quality assurance programs.

I would also like to expand on a couple of things that Dr. Ben Eiseman brought up.

There are certain flaws in our current scoring system. One of them is the unavailability of a good scoring mechanism to be used for surgical patients. The only one that has been developed for surgical patients is Dr. John Siegle's from Baltimore. Unfortunately, that system is so complex it is unusable in a community hospital. The system is so complex it cannot be used and so its utility in research is marginal. Therefore we need a simple scoring mechanism; however I have reservations whether a scoring mechanism could be used for anything other than cost containment. The other flaw that I wish to address is the quality assurance in our surgical intensive care units.

Dr. Dennis O'Leary has said that JCAHO will focus on outcome measurements. To me the best way to look at outcome is through a standard morbidity and mortality conference.

Unfortunately, M & M Conferences are not done well in the community hospitals because in most instances it is a whitewash. People aren't willing to stand up and criticize their peers or at least take a hard look at true morbidity and mortality issues. Until we can do that, as an organized surgical body, I think we are going to be criticized by HCFA and other government agencies.

The bottom line is that this study is excellent. I urge all of you to support the concept that HCFA cannot foist these criteria on us.

DR. CHARLES E. LUCAS (Detroit, Michigan): Dr. Civetta, your analysis is based on two accurate collections of data; namely the critical care scoring system and the cost assessment. The other discussants have highlighted the imperfections of the scoring system.

I would like to have you comment on the accuracy of the cost system. I don't think there is a hospital in the country that knows the cost of patient care, and in that lack of knowledge of what patient care costs, the hospitals come up with hospital charges that are incorrectly based on their utilization of hospital resources.

Now you know that in the intensive care unit a patient who is very, very sick requires a great deal of nursing and physician time, whereas the patient who is not so sick will take much less time. Yet, the hospital charge is based on an average of the total cost of the intensive care unit, which is then billed out the same for each patient.

This completely destroys a scientific analysis regarding cost. I would like for you to comment on the accuracy of your hospital charge as it truly reflects costs to the medical system.

DR. JOSEPH M. CIVETTA (Closing discussion): I have always counted myself as an enthusiast in the creation of scoring systems, having been involved with the creation of the therapeutic intervention scoring system and another one based on diagnosis. It was only later that I realized that all have a false classification rate of approximately 15%. All gave up on prediction of outcome for individual patients, but now they have gone to these other areas of cost containment and quality assurance that are even more threatening, I think, in some ways.

In response to Dr. Demling's question about another assessment tool, I do not think that we ought to go ahead and create individual ones in each hospital. A nationally applicable one would be desirable. The characteristics of the national one in today's world must be more than just outcome. It must be based on hospital costs and particularly days in the ICU, because that is clearly the most important way that we, as ICU directors, ration care. When a bed is vacated, then you can use it again. If a patient is in a bed for 90 days, that uses the same resource as an elective surgical service that has 90 different patients in the same bed for 3 months. We need predictors of long-term users of bed days and of resources, not just outcome. The problem is that those two items are consumed by patients who develop sepsis and there are many sepsis scores already in existence. Most of them are pretty complicated, and none of them is any more beneficial on admission. The other major problem is, of course, multiple organ system failure, and many of those patients will have normally functioning systems on admission, and therefore, one cannot predict what is going to happen later. I hope that you will lend support to the ACS Task Force to develop a new and important means of assessing surgical patients.

For Dr. Drucker, I think it is extremely important to point out that this system is terribly deficient in terms of trauma patients. In fact, in one of the APACHE coefficients, we noted in the Task Force this summer that a head injury had a positive coefficient instead of a negative one, which would indicate a lessened survival. I do not think they have the same kind of head injury patients.

In terms of treatment in the ER and the pre-ICU treatment, this again is supposed to be included in APACHE III, but even so, it is not going to be correct because it doesn't take into account preventive care. For

instance, in an urban trauma system with a short transport time, the patients never develop shock or acidosis or so forth, but still have a major injury. It also fails to reflect individual goals of treatment that are different. For instance, if you choose to operate on a patient and use hemodilution, hypothermia, and controlled hypotension, then your patient will accrue a lot of APACHE points, but as soon as you reverse all those things they are 'better' and that accounts for the fact, I think, that coronary artery bypass graft patients have been excluded from analysis, because APACHE II predicted extremely high mortalities, and as we know, the mortality rates are very, very low.

As far as the sequential APACHE scores, we have reported on them previously and it is in the manuscript as well. The long-term patients, who make up about 7% of the patients, but consume 35% of the bed days, were divided into patients who lived and patients who died. We then analyzed their numbers separately. The APACHE scores completely overlap for the first seven days, but even more importantly, the expected mortality rate in the group that all ultimately died was predicted on admission to be 20%, and the day before each died, the predicted mortality rate was 35%, so sequential APACHes do not help us either.

There has been a new approach from Dr. Chang in Saudi Arabia using an algorithm for sequential scores. In our own patients, this algorithm only identifies a small number of patients who were terribly ill, and by the time the algorithm predicts mortality, most patients die, and so it would not save any bed days. The only important group of patients are long-term patients who spend 1 to perhaps 3 and 4 months. Those are the ones who use the bed days.

As far as Dr. Eiseman's question, developing a system for monitoring is really not terribly important because the usage is very low in terms of the total number of bed days that we actually provided. We did a study in which we looked at patients who were given preoperative ICU consults and then at the end of the operation if the surgeon, the anesthesiologist, and the intensivist felt that all went well and the patients were stable, about 30% of those patients were sent to the recovery room. When we looked at total hospital days and total hospital bills, the lack of that one day of prophylactic ICU care did not affect their hospital bill, so there is not any money to be saved by excluding stable elective patients. I say that we ought to keep those patients in the ICU where they can receive appropriate observation. Then, if something does go wrong, we can step in and treat quickly and, I hope, more effectively.

In response to Dr. Lucas, we have all worried about this problem, that is, after the years and years of creative accounting, being able to go back to costs from what is being charged. I gave up at that in our hospital some years ago when we first started doing studies, and the only hard number we can reproducibly obtain is hospital charges. The only thing you can say is that there is some relationship between charges and costs, certainly not profit, in our hospital.

Tracheobronchial Obstructions in Infants and Children

Experience with 45 Cases

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Forty-five infants and children with intrathoracic tracheobronchial obstructions requiring surgical treatment are reported. Segmental stenosis of the trachea is defined as involvement of less than one half the length of the airway, which affected six infants. Elongated stenosis involving more than one half the length of the trachea was seen in 12 infants, and complete annular cartilage rings, along the entire length of the trachea, were present in 11. Severe tracheomalacia occurred in six infants associated with aortic arch anomalies and in nine infants with esophageal atresia. Segmental tracheal resection was performed in 17 cases (two after failure of a rib cartilage graft), and anastomotic stricture developed in three. These three anastomotic strictures were resected, resulting in an excellent airway in two and resticture in one. Rib cartilage grafts were used in five patients: two of three with elongated stenosis with complete tracheal rings required subsequent resection, and one of two infants with tracheomalacia had excellent outcome. Approximately 50% of an infant's trachea can be resected, but rib cartilage grafts should be used for elongated stenosis. Resection of bronchial stenosis in two patients resulted in a widely patent bronchus. From this experience primary segmental tracheobronchial resection and re-resection of recurrent stenosis are highly successful. Anastomotic stricture is due to tension at the suture line and suture material inciting a fibrotic reaction. Rib cartilage grafts amounting to 25% or less of the circumference of the airway readily resurfaces with adjacent epithelium, but when 30% or more of the circumference is rib graft, epithelialization may be impaired.

WE HAVE ENCOUNTERED 45 infants and children with high-grade intrathoracic tracheobronchial obstructions. This report is an expansion of our experience published in 1982.¹ Most of these obstructions are surgically correctable, and this has resulted in an increasing frequency of referral. Nevertheless the diagnosis is often delayed, and death during transport and preoperative assessment can be prevented by recognizing the urgency of treating even apparently mild airway obstructions. The small size of the airway in infants

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limits any margin of safety; for example, 0.25 mm of mucosal edema in a 3-mm diameter trachea results in reduction in the cross-sectional area by more than 30% and a diminished air flow of more than 50%. Infants and children with inspiratory and expiratory stridor, increased work in breathing exhibited by chest wall retractions, and prolonged expiration, with or without cyanosis, should have prompt diagnostic evaluation of the airway.

Materials and Methods

We have reviewed our case experience of infants and children seen at the University of California, San Francisco, from 1966 through 1989 in which intrathoracic tracheobronchial obstructions were identified.

Diagnosis

Our diagnostic assessment is detailed in a previous publication.¹ Since this report we attempt to visualize beyond the area of stenosis by using an ultrathin flexible bronchoscope, with an outside diameter of 3 mm, or a Storz optical bundle, 3 mm in diameter, that can be passed beyond the end of the rigid Storz bronchoscope (Carl Storz, Instrument Co., Culver City, CA). The flexible bronchoscope is used during operation by passing it through an elbow connector of an endotracheal tube, which allows continuous ventilation of the patient. Children who did not seem to have critical airway narrowing were sedated with morphine and/or midazolam, and topical lidocaine was sprayed onto the nasopharynx, larynx, and trachea. The flexible bronchoscope could be passed through the nasopharynx and into the trachea while the patient was breathing spontaneously, and this approach was especially helpful in evaluation laryngomalacia, abnormal vocal cord function, and tracheomalacia. We de-

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terminated the narrowest diameter of the airway by the outside diameter of the bronchoscope or endotracheal tube, which would and would not traverse the most stenotic area.

Cine computed tomography (cine CT scan) produces 10- to 0.3-mm thick transverse images per second. Because of the rapid imaging, this study can be performed without anesthesia or sedation, and it is useful to outline the length of the tracheobronchial narrowing in older children (Fig. 1). However, in one infant with a normal length of trachea, the cine CT suggested a short segmental stenosis when the narrowing with complete rings had actually involved more than one half of the tracheal length.

Surgical Treatment

Access to the trachea and major bronchi for tracheal resection was through a median sternotomy. A posterolateral thoracotomy on the side opposite the aortic arch was used when there seemed to be an abnormally elongated trachea. The cardiopulmonary oxygenator was used in only one case. We prefer to ventilate the patient by introducing an endotracheal tube into the distal trachea or a main bronchus after the tracheal incision. Traction sutures of 2-0 silk are placed in the lateral edge of the cartilage rings proximal and distal to the proposed segment of trachea to be resected, and this helps to mobilize the tracheal ends and to take tension off the suture line (after Grillo²). When a segmental resection is performed, we transect the trachea at the distal point of stenosis initially, and we serially cut across the trachea until a satisfactory lumen is encountered. A range of sterile endotracheal tube sizes and connecting tube is made available on the operating table, and the distal trachea or either bronchus is cannulated with the size tube that allows full expansion of the lung with little air leakage. The connecting tubing is passed to the anesthesiologist, and the effectiveness of ventilation can be monitored by cutaneous oxygen saturation and arterial blood gas analysis. We mobilize only the portion of the trachea to be resected to avoid impairing the blood supply to the remaining trachea. The proximal level for transection of trachea can be detected by (1) advancing the appropriate-sized translaryngeal endotracheal tube, (2) by intraoperative bronchoscopy and by visualizing the light through the trachea, or (3) by serially transecting the trachea until the ideal lumen size is encountered.

The anastomosis is accomplished by placing sutures through the cartilage rings adjacent to the point of transection about 3 mm apart. The head and neck of the patient are then flexed and the traction sutures are used to pull the tracheal edges together while the anastomotic sutures are tied in sequence from posterior to anterior. The

distal endotracheal tube is removed as the anterior anastomotic sutures are tied, and ventilation is resumed through the proximal endotracheal tube. We try to avoid entering the lumen with these sutures and the knots are tied on the outside to minimize granulation tissue formation. With completion of the anastomosis, the lateral traction sutures bridging the anastomosis are tied to minimize distraction of the suture line.

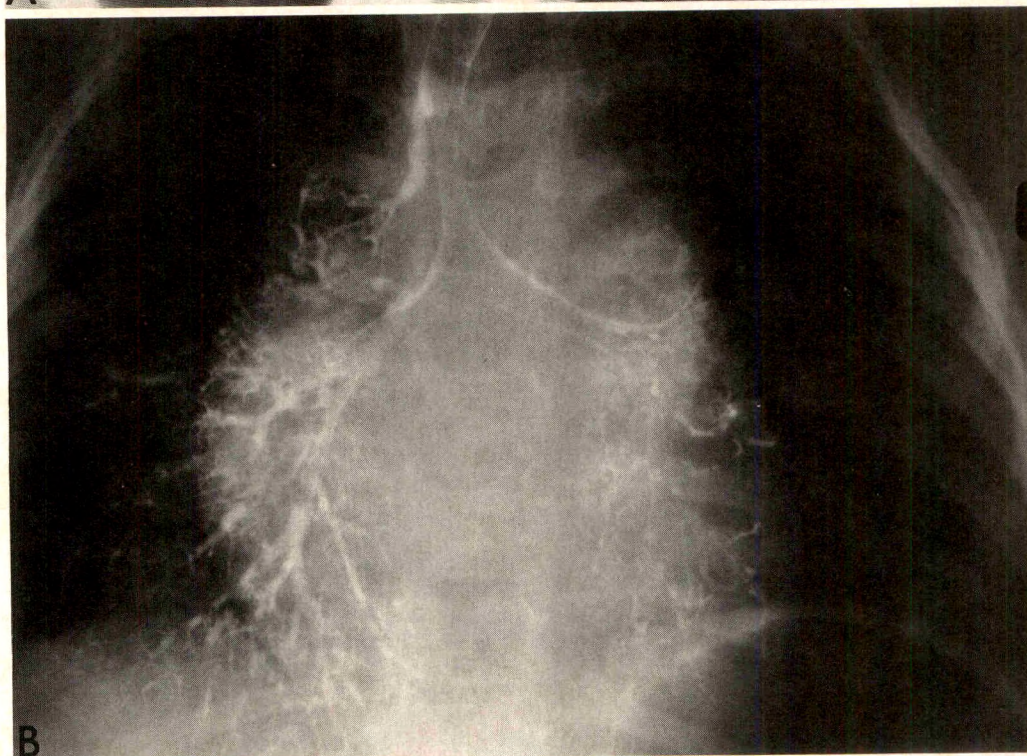
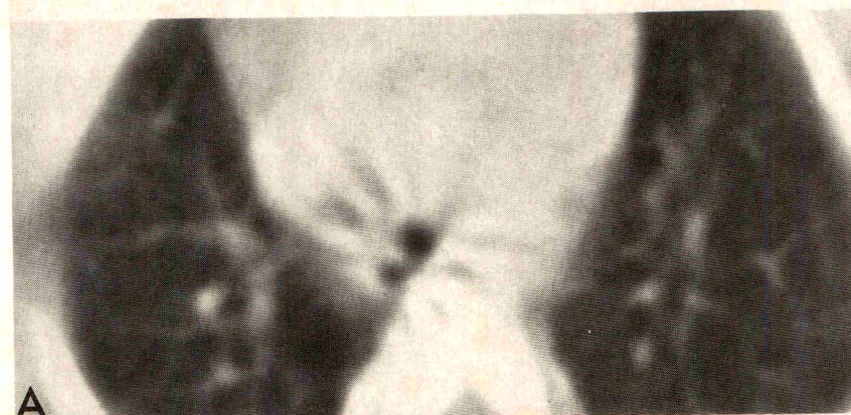
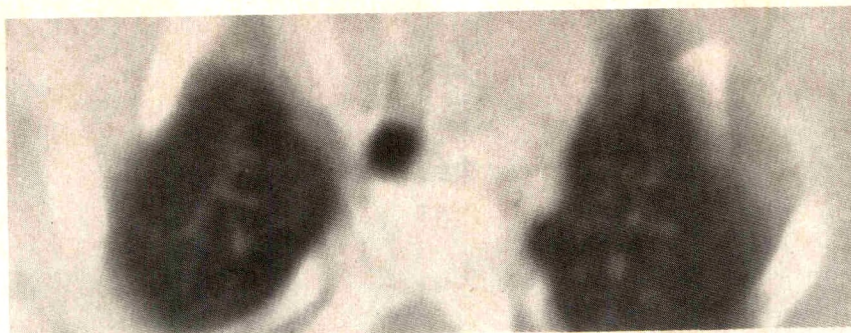
For elongated tracheal stenosis, involving more than one half the tracheal length, we used a wedge graft of cartilage taken from the costal cartilage of the fifth or sixth rib.³⁻⁶ In removing the costal cartilage, the perichondrium was left on the flattest surface, where it is placed on the lumen side of the trachea to encourage growth of mucosa across the surface. When the rib cartilage is removed, it is trimmed in a wedge shape and tapered at the ends along a length slightly greater than the length of the incision in the trachea. Only the anterior surface of the trachea is dissected along the entire length of the narrowing to avoid interfering with the blood supply. When the wall of the trachea is being incised for the rib cartilage graft, the appropriate-sized translaryngeal endotracheal tube can be advanced into the distal trachea or bronchi, and the tube can serve as a means of identifying an optimum size to reconstruct the airway. The trimmed costal cartilage is then aligned to the defect and sutures are placed approximately 3 mm apart so the inner surface does not protrude into the lumen.

With completion of these anastomoses, the wound is filled with Ringer's solution and high-pressure ventilation is given to detect the presence of an air leak. We do not use a mediastinal drain.

After operation the head and neck are maintained in a flexed position by using a custom-molded brace from the occiput of the head to the lower thorax. The patients are extubated as early as possible, preferably in the operating room, to minimize mucus plugging from dried secretion and to lessen trauma from endotracheal suctioning.

One 22-month-old child (patient 9) had an especially elongated, and very narrow trachea with complete tracheal rings. We hoped to resect a long section of the trachea, with minimal tension on the suture line. The tension was to be relieved by extensively mobilizing the lung hila and by dividing the inferior pulmonary ligament on each side, while the patient was on cardiopulmonary bypass. This extensive dissection did not allow more proximal position of the carina. One third of the mid-portion of the trachea was resected and the anterior wall of the remaining stenotic trachea from the carina to the thoracic inlet was incised. We used a pericardial patch graft because the length of the tracheal defect seemed to be greater than a cartilage graft would supply. The pericardial patch pro-

FIGS. 1A and B. Cine CT and bronchogram of a 3.5-year-old girl who had segmental stenosis from complete tracheal rings. She was having increasing respiratory insufficiency since the age of 4 months. (A) Cine CT of the upper chest demonstrates a normal trachea, while the image in the lower thorax, distal to the anomalous origin of a right upper lobe tracheal bronchus, shows significant narrowing. (B) Bronchogram of the same patient is shown for comparison. The narrowest tracheal diameter was 5 mm, between the tracheal bronchus and the carina. Note the tracheal bifurcation is a broad angle, arising at the level of T-6.



duced a very floppy airway, which required endotracheal ventilatory support for 3 weeks. Subsequent contraction and narrowing of the pericardial patch required dilation of the trachea at 4 weeks and 7 weeks after operation. He

has persistent noisy breathing 8 years after operation, and because he resides a long distance from us, follow-up pulmonary function has not been possible. Encephalopathy after a preoperative hypoxic episode limits his mobility.

TABLE 1. *Congenital Tracheal Stenosis*

Patient Sex	Age and Birth Weight	Age at Operation	Narrowest Tracheal Diameter	Associated Anomalies	Treatment	Results
Segmental Complete Rings						
1. Male	Newborn 3100 g	16 months	3 mm	None	Sternotomy resect 2.7 cm midtrachea 5.0 nylon	Excellent airway bronchoscopic removal nylon
2. Male	Newborn 2950 g	17 days	3.5 mm	Tetralogy of Fallot	Sternotomy resect 1.7 cm 6 rings 5-0 PDS	Excellent airway tetralogy repaired at 34 days
3. Female	Newborn 2670 g	6 weeks	3 mm	Agenesis left lung	Sternotomy resect 1.5 cm 5-0 PDS	Excellent airway
4. Female	4 months	3.5 years	5 mm	Right upper tracheal bronchus, long trachea to T-6	Posterolat. thoracotomy resect 2.4 cm. 4-0 PDS	Excellent airway
Segmental Incomplete Rings						
5. Male	Newborn 1500 g	3 months	2 mm	Membranous stenosis, 1.5 cm proximal to carina Diverticula right and left main bronchi Hyaline membrane disease	Bronchoscopy KTP laser excision stenosis	No recurrent stenosis, prolonged ventilatory support for severe reactive airway disease; bronchomalacia; bronchopulmonary dysplasia tracheostomy for CPAP-14 cm. H ₂ O pressure
6. Female	Newborn	4 years	4 mm	Right phrenic palsy preop.	Right postlat. thoracotomy resect 1.5 cm stenosis	Excellent airway
Elongated Complete Rings						
7. Male	Newborn 3200 g	4 months	4 mm	Complete rings, entire trachea	Sternotomy tracheal incision 3.5 cm—rib cartilage graft 6-0 nylon suture	Poor airway recurrent granulation Nd Yag Laser excision — Tracheal resection at age 7 mos—8 rings 2.5 cm 4-0 PDS —
8. Male	Newborn 2900 g	15 months	3.6 mm	Trisomy 21 agenesis left lung, complete rings entire, long trachea bronchus	Sternotomy rib cartilage graft 6.5 cm. 5-0 PDS	Excellent airway Poor airway, recurrent granulation KTP laser excision — Tracheal resection at age 23 months 4 cm 4-0 PDS —
9. Male	Newborn 2800 g	22 months	3.6 mm	13 ribs; posturethral valves Long trachea to T-7 6.5 cm	Sternotomy cardiopulmonary bypass resect 2.5 cm Pericardial graft 1.75 cm. wide 5-0 polypropylene	Excellent airway Intubated 1 month; hypoxic encephalopathy, good airway
10. Male	Newborn	19 days	2 mm	Left diaphrag. hernia repaired — Age 2 months G-E reflux Fundoplication; right upper lobe tracheal bronchus trifurcation	Sternotomy resect 9 rings 5-0 PDS	Anastomotic stricture — Stricture resected at age 4 months 4-0 PDS — Excellent airway
11. Female	Newborn 3500 g	18 days	2 mm	Anomalous left innominate artery; long trachea; right upper tracheal bronchus	Sternotomy resect 1.5 cm	Died with residual stenotic distal trachea and main bronchi
12. Female	Newborn 4000 g	None	2.5 cm	Long trachea 7.6 cm 24 complete rings, anomalous left pulmonary artery	None	Died age 24 hours during transfer
13. Male	Newborn 3000 g	23 weeks	3.6 cm	Anomalous left pulmonary artery; long trachea to T-7	Right postlat thoracotomy, Resect 2.5 cm. 4-0 polyester	Poor airway; intubated for 5 weeks discharged 7 weeks postop.; respiratory arrest at 35 weeks Residual stenotic complete rings, anastomotic stricture; died at 48 weeks

TABLE 1. (Continued)

Patient Sex	Age and Birth Weight	Age at Operation	Narrowest Tracheal Diameter	Associated Anomalies	Treatment	Results
14. Female	Newborn 2700 g	2.5 mos	2 mm	Anomalous left pulmonary artery long trachea	Right postlat. thoracotomy, division pulmonary artery	Hypoxic during operation; bled from divided pulmonary artery; died from severe tracheobronchitis
15. Female	Newborn 2650 g	None	2 mm	Multiple vertebral anomalies; single, hydronephrotic left kidney; all tracheal rings fragmented; no membranous trachea, right pulmonary hypoplasia	None	Died age 72 hours during transfer
16. Male	Newborn 3560 g	None	3.6 mm	Agenesis right lung; 2 left pulmonary arteries, Complete ring stenosis from cricoid to upper/lower lobe bronchi	None	Respiratory failure; intubated at age 4 months — Operation canceled for chicken pox; ventilated at 20 days — Died 1 day preop: granulations occluded airway
17. Male	Newborn 3150 g	None	5 mm	Complete rings 4.5 cm long, 2.5 cm proximal to carina; right upper lobe tracheal bronchus	None	Raspy inspiratory-expiratory breath sounds; normal exercise tolerance at 22 months; no surgical correction 1985; recurrent pneumonia 1987–1989
18. Male	Newborn 3220 g	None	2 mm	Chondrodysplasia punctata; calcified epiphysis, calcified and stenotic larynx, cricoid, trachea, main bronchi; normal tracheal membrane; normal secondary bronchi	None	Died after ventilator support was withdrawn
Tracheomalacia with Vascular Ring						
19. Male	6 wks 3200 g	14 months	Normal membranous trachea	Situs, inversus A–V canal; mitral insufficiency, interrupted inferior vena cava, polysplenia, bilateral left bronchial configuration, anomalous left-sided origin innominate artery compressing and displacing trachea posteriorly and to right	Age 3.5 months A–V canal repair postop. intubated ventilatory support for 1 month — Age 14 months, left thoracotomy divide innominate artery with 12 mm Gortex graft from aorta —	Good airway
20. Female	Newborn 2450 g	8 weeks	Normal membranous trachea	Severely deformed tracheomalacia Right aortic arch; L-transpositions tricuspid atresia pulmonary stenosis	Resect 6 indented tracheal rings 2 cm long 4-0 Teflon External rib strut support	Good airway; died at 11 months from cardiac anomaly
21. Female	Newborn 3150 g	2 weeks 8 months	Normal membranous trachea	Double aortic arch	Age 2 weeks; division left aortic isthmus — Age 8 months, left thoracotomy; resection 3 tracheal rings, 1.5 cm 5-0 polyethylene	Excellent airway, hypoxic encephalopathy due to respiratory arrest at age 6 months
22. Male	Newborn 3250 g	3 months 3.5 months	Normal membranous trachea	Double aortic arch	Age 3 months, left thoracotomy; divisions left aortic isthmus postop. Required endotracheal ventilatory support	Excellent airway

TABLE 1. (Continued)

Patient Sex	Age and Birth Weight	Age at Operation	Narrowest Tracheal Diameter	Associated Anomalies	Treatment	Results
23. Male	Newborn 3100 g	21 months	Normal membranous trachea	Anomalous origin innominate artery compression trachea from carina to thoracic inlet	— Age 3.5 months, right thoracotomy; mobilization compressing right aortic arch; resection 4 tracheal rings, 1.5 cm 4-0 PDS Median sternotomy aortoinnominate artery pexy; intraop. bronchoscopy, no improvement; rib cartilage graft carina to thoracic inlet; 4-0 PDS	Good airway — Slight compression at the carina
24. Female	Newborn 3630 g	21 months 6 weeks 6 months	Normal membranous trachea	Double aortic arch	Age 1 month left thoracotomy divide left aortic isthmus- required continued ventilatory support — Age 6 weeks left thoracotomy resected 1 cm distal trachea 5-0 nylon — Age 6 months resected stricture 5-0 nylon	Continued obstructing airway from residual extensive tracheomalacia requiring tracheostomy Died tracheostomy plug age 8 mos
25. Male	Newborn 2600 g	Newborn 6 weeks 2 months 6 months 11 months	Normal membranous trachea	Tracheomalacia with Esophageal Atresia Esoph. atresia TEF high imperforate anus Gastroesophageal reflux	Repair esophageal atresia/ colostomy — Age 6 weeks fundoplication — Age 2 months aorto pexy — Age 6 months tracheostomy — Age 11 months rib cartilage graft from carina to thoracic inlet	Excellent airway
26. Male	Newborn 3420 g	Newborn 2 months 3 months 7 months 8 months 9 months 35 months	Wide membranous trachea	Esophageal atresia TEF. high imperforate anus coarctation aorta vertebral anomalies	Age 2 months repair esoph. atresia/colostomy — Age 3 months patch aortopexy — Age 7 months tracheostomy — Age 8 months rib cartilage graft tracheoplasty — Age 9 months, long tube tracheostomy continuous positive airway breathing (CPAP) — Age 35 months, closure tracheostomy	Poor airway progressive tracheomalacia extending into bronchi required CPAP 2 + yrs. Currently good airway with normal exercise tolerance
27. Male	Newborn 3200 g	Newborn 6 weeks 3 months	Wide membranous trachea	Esophageal atresia TEF	Repair esoph., atresia, TEF age 6 weeks — Tracheostomy long tube at age 3 months — Closure tracheostomy	Repeated airway obstructive episodes with cyanosis not improved with tracheostomy; gradual improvement with growth age 1 year

TABLE 1. (Continued)

Patient Sex	Age and Birth Weight	Age at Operation	Narrowest Tracheal Diameter	Associated Anomalies	Treatment	Results
Acquired Tracheal Stenosis						
28. Female	3 years	10 years		None; severe asthma attacks since age 3 yrs, repeated intubation for ventilatory support over 7 years for asthma	Bronchoscopic excision 1.5 cm, midtracheal stenosis due to granulation and fibrosis	Excellent airway; asthma improved
Tumor of Trachea						
29. Female	3.5 years	4 years 4.5 years		Hamartomatous polyp 2 cm proximal to carina	Age 4 years, bronchoscopy removal of polyp — Age 4.5 years resection 2 cm length of trachea for recurrence 4-0 nylon	Excellent airway required bronchoscopy removal nylon suture with granulomas
Congenital Bronchial Stenosis						
30. Male	Newborn 3550 g	4 years	4 mm	Funnel-shaped narrow left main bronchus by prominent corrugated mucosal bands, lingular bronchietasis	Bronchoscopic resection with cautery resection of lingula	Raspy breath sounds, no restenosis
Acquired Bronchial Stenosis						
31. Female	Newborn 1900 g	6 weeks	Occluded	Hyaline membrane and bronchopulmonary dysplasia; required prolonged endotracheal ventilatory support Repeatedly intubated right main bronchus resulting in granulation/cicatrical stenosis; repeated atelectasis and hyper inflation right lung	Bronchoscopic debridement of granulation and dilatation right main and intermediate bronchus	Normal airway
32. Male	2 years 2680 g	2.5 years	4 mm	Long gap esophageal atresia TEF, high imperforate anus developed recurrent right pneumonia	Following stage repair of esophageal atresia, required tracheostomy for recurrent nerve palsy. Developed stenotic right bronchial stenosis from suction trauma age 2.5 years — Sleeve excision 3 bronchial rings 4-0 PDS	Excellent airway
33. Female	Newborn 2900 g	9 months	2 mm	Esophageal atresia. Left main bronchus accidentally transected and anastomosed. Recurrent pneumonia left lung	Age 9 months sleeve excision 3 bronchial rings 4-0 PDS	Excellent airway

PDS, polydioxamone; TEF tracheoesophageal fistula.

Results

The details of the patients with tracheobronchial obstructions are shown in Table 1. The results of treatment

are graded as excellent, good, or poor. Excellent outcome means that there is no apparent impairment of air passage based on prolonged exercise tolerance, and no abnormal chest wall retractions or breath sounds. Good results

means that there is no impairment of breathing with exercise, although there may be some evidence of chest wall retractions at the end of exercise or very loud, raspy breath sounds indicative of turbulent airflow. Poor results means that significant airway obstruction persisted or recurred after operation, resulting from obvious stenosis that was subsequently identified endoscopically.

Tracheal Atresia

Of the four infants with tracheal atresia, the bronchi of two entered the esophagus directly and in two instances there was a short distal trachea communicating with the esophagus. All patients weighed less than 2800 g and they all had multiple cardiac anomalies. This lesion was readily recognized because an endotracheal tube would not pass beyond the vocal cords and there was no trachea palpable when examining the neck. The lungs could be ventilated by way of an endotracheal tube in the esophagus. We attempted a tracheostomy in one, which proved the absence of trachea. All of these infants died shortly after birth. With present technology, correction of tracheal atresia requires a sufficient length of distal trachea to be approximated to the neck for tracheostomy. There is no method of providing a rigid, wide-open airway lined by ciliated epithelium that would convey mucoid secretions to the level of the neck or larynx.^{7,8}

Tracheal Stenosis

We noted two broad categories of tracheal stenosis: (1) congenital anomalies, and (2) those acquired from trauma, infection, or tumor. Of the congenital tracheal stenoses, we have identified two categories: segmental stenosis, involving 50% or less of the length of the trachea, and elongated stenosis. Segmental stenosis was associated with complete annular cartilage rings in four patients and incomplete tracheal rings with an intact membranous portion of the trachea in two patients. Elongated tracheal stenosis was associated with complete tracheal rings in 11 patients. One infant had chondrodysplasia punctata in which the cartilage of the trachea, larynx, and major bronchi were calcified.⁹ There was severe tracheal stenosis from the carina to the cricoid cartilage with an intact tracheal membrane.

Of the 18 patients with congenital stenosis, 11 were male and 7 were female. Symptoms of inspiratory and expiratory stridor were present at birth in each infant, and referral for treatment varied from birth to 3.5 years. Most of the patients displayed severe respiratory obstruction within 3 months. Associated anomalies were present in all but one infant. The most common airway anomaly, present in 5 of the 18 patients, was a right upper lobe

bronchus originating on the trachea or at the bifurcation of the right and left main bronchi. Five patients had an anomalous left pulmonary artery sling. Three had agenesis of one lung; one was right and two were left lungs. Two infants had right pulmonary hypoplasia. We did not routinely count the number of tracheal rings in these patients, but we noted that the carina was at the level of the sixth and seventh vertebrae by chest roentgenograms in four infants, indicative of an abnormally long trachea. Tetralogy of Fallot, posterolateral diaphragmatic hernia, anomalous origin of the innominate artery far to the left of the midline, and chondrodysplasia punctata were noted in one patient each.

Infants with significant obstructive airway symptoms require urgent attention. Four infants died before surgical correction could be performed, 24 hours to 4 months from the onset of severe obstructive symptoms beginning at birth. For example one child (patient 16) with agenesis of the right lung, complete tracheal rings, and pulmonary artery sling developed progressive respiratory insufficiency requiring intubation at 4 months. A 4.0-mm (outer diameter) endotracheal tube could not be advanced beyond the upper trachea. Transfer to our hospital for thoracotomy was planned for the next morning when the patient developed chicken pox. He was ventilated for 20 days when he died from an obstructed trachea due to endotracheal tube-induced granulation occlusion of the airway.

Operative correction was performed in 13 patients, and one had not been treated because he did not have critical airway narrowing (patient 17; see Note Added in Proof). Segmental tracheal resection was accomplished initially in eight patients, and rib cartilage or pericardial patch grafts were used in three. Five of the eight infants with segmental resection have excellent airways, and two developed anastomotic stricture. The stricture was resected in both patients. One stricture (patient 10) was clearly related to excessive tension on the anastomosis when 50% of the trachea was resected. After re-resection of the stricture, he has an excellent airway. The other infant (patient 13) had a very elongated and narrow lumen, less than 3.6-mm diameter, with complete rings involving the entire trachea. After resection of 2.5 cm of the most stenotic area, stricture recurred. In retrospect this patient should have been treated by a longitudinal tracheal incision and a wedge cartilage graft. This infant had respiratory support withdrawn when severe hypoxic encephalopathy was recognized by CT scan of the brain. One infant died (patient 14) during operation before a satisfactory airway could be established, and another infant (patient 11) died shortly after operation from persistent airway obstruction when we failed to recognize residual complete ring stenosis of the trachea beyond the right tracheal bronchus.

Two of the thirteen patients with congenital stenosis

(patients 7 and 8), in whom there was elongated, very narrow trachea, composed of complete rings along the entire length of the trachea, were treated with wedge rib cartilage grafts. Three others (patients 12, 15, and 16) would have had the cartilage grafts had they survived to go to the operating room. Both of the patients with the cartilage grafts developed recurrent granulation tissue in the narrowest area of the airway. Repeated Nd:YAG or KTP laser excision of the granulations was required and epithelial growth from the native edges of the trachea did not occur. A subsequent resection of the distal trachea (2.5 and 4.0 cm long), each representing approximately 40% of the tracheal length, resulted in excellent airways. The pathology specimens in these cases showed resorption of the cartilage and a fibrous membrane that was not dissimilar to the normal membranous trachea (Fig. 2).

Tracheomalacia

Sixteen patients had such severe tracheomalacia that surgical treatment was necessary. We noted that these patients fell into two broad categories: (1) those related to aortic and branch vessel compression, and (2) those associated with esophageal atresia.

Tracheomalacia associated with aortic arch and branch vessel anomalies required surgical treatment in six patients. Three children had double aortic arch compression of the trachea, which failed to improve after division of

the aortic ring because of segmental buckling and infolding of the tracheal rings above the carina. These three patients had a resection of three to four distal tracheal rings. Two had an excellent result, while one (patient 24) required re-resection of the stricture.

One 6-week-old child (patient 19) had an innominate artery clearly arising far to the left of the midline, displacing the trachea posteriorly and to the right. The innominate artery was divided and replaced by a Gortex tube graft. Intraoperative bronchoscopy showed persistent infolding and stenosis of the distal trachea. Therefore six distal tracheal rings were resected, resulting in an excellent airway.

One infant (patient 20) with severe tracheomalacia associated with a right aortic arch and an L-transposition of the heart had a fourth rib strut sutured to the tracheal rings, which produced a greatly improved airway.¹⁰ When she died 9 months later from her heart disease, the rib strut had completely resorbed.

A 21-month-old child (patient 23) with progressive tracheomalacia and anomalous origin of the innominate artery was not improved by an aorto-innominate artery pexy as assessed by intraoperative bronchoscopy. The membranous trachea was normal, but there was indentation along the entire anterior length of the intrathoracic trachea. Therefore a rib cartilage graft was placed from the carina to the thoracic inlet, which resolved the infolding tracheal rings.

FIG. 2. Photomicrograph of a cross-section of a trachea, originally composed of complete rings, which was split longitudinally for placement of a rib cartilage graft 3 months earlier. Note the normal cartilage graft is stained with hematoxylin (open arrow) while most of the grafted rib cartilage has resorbed with a small amount of residual degenerating cartilage (closed arrow), leaving a membranous portion. Granulation tissue was cauterized with an Nd:YAG laser just before this resection, which destroyed the surrounding epithelial lining. Note that submucosal glands have migrated over to the membranous portion. The membranous portion accounts for one third of the circumference of this area of the trachea.



Severe tracheomalacia associated with esophageal atresia was treated in nine infants (approximately 5% of our cases with esophageal atresia). These patients had repeated episodes of apnea and bradycardia during eating and crying. All nine infants had an aortopexy.¹¹ This procedure worked very well in six, but in three patients additional operative procedures were necessary. In each case the aorta and innominate artery were already adjacent to the sternum. These three infants had a tracheostomy that proved to be ineffective because the malacia extended beyond the end of the tube. Therefore, in one infant (patient 25), we tried an extraluminal rib strut, sutured to the cartilage rings along the length of the intrathoracic trachea.¹⁰ Because of persistent severe malacia, a rib cartilage graft was placed in the anterior wall of the trachea, and it proved to be very effective in stiffening the airway. This patient had a normal membranous portion of the trachea. Because of this success, we tried a long rib cartilage graft in the next infant (patient 26) who failed aortopexy, but this was ineffective because he had an abnormally wide, redundant membranous trachea that continued to collapse into the lumen.¹³ In addition he developed progressive bronchomalacia, and by the age of 9 months he required a tracheostomy to administer continuous positive airway pressure breathing up to 12 cm water pressure to keep his airways open.¹² After 2 years his airways no longer collapsed and the tracheostomy was closed. In the third infant (patient 27), the tracheostomy did not improve his breathing because the lumen tended to become occluded by an abnormally wide, redundant and floppy membranous portion of the trachea. He required prolonged hospitalization with continuous positive pressure breathing to treat repeated cardiorespiratory arrest, but he is gradually improving from his airway obstructive episodes as he grows.

Acquired tracheal stenosis from trauma was encountered in only one of our patients (patient 28). She had severe asthma attacks and was repeatedly intubated for ventilatory support several times a year from the age of 3 to 10 years. A 1.5-cm-long stenosis from granulation and fibrosis responded to bronchoscopic excision and dilatation of the stenotic area.

One 4-year-old patient developed a hamartomatous polyp in the distal trachea (patient 29). After polypectomy recurrence at the base required a wedge resection of the distal trachea with excellent results.

Bronchial Stenosis

Bronchial stenosis seemed to be congenital in one patient and acquired in three. Recurring left-sided pneumonia in a 4-year-old child (patient 30) required bronchography, which showed prominent spiral mucosal bands along the mid portion of the left main bronchus and

bronchiectasis of the lingula. The mucosal bands were cauterized and the lingula was resected with excellent long-term results. Two of the acquired bronchial stenoses followed repeated endotracheal suctioning. One (patient 31) responded to bronchoscopic debridement and dilatation of the stenotic right main bronchus and the other (patient 32) required excision of three bronchial rings with primary anastomosis. A third child (patient 33) had accidental transection of the left main bronchus in the course of repairing an esophageal atresia with tracheoesophageal fistula. The left main bronchus was apparently confused with the tracheoesophageal fistula. The bronchus had been repaired but stenosis ensued. This was repaired by excision of three bronchial rings and primary anastomosis with excellent results.

Discussion

Approximately 50% of patients with a pulmonary sling will have complete tracheal rings that are stenotic.^{14,15} Of our 15 patients with constricted complete tracheal rings, five had an anomalous left pulmonary artery. When a pulmonary artery sling is diagnosed, bronchoscopy should be performed to detect intrinsic complete tracheal ring stenosis before attempting to divide and repair the anomalous vessel. If there is intrinsic stenosis, excision of the tracheal stenosis will allow displacement of the anomalous pulmonary artery to the left. Repair of the stenotic airway is achieved without the need for pulmonary artery reconstruction.

Double aortic arch and anomalous position of the major branches of the aorta can also be identified by echocardiography. Tracheomalacia is usually associated, and we prefer making a video recording during flexible bronchoscopy before operation, while the patient is breathing spontaneously, to determine the extent and length of airway obstruction. When the airway obstruction requires surgical treatment of the aortic arch anomaly, intraoperative bronchoscopy should be performed because significant airway narrowing may persist, and aorto-innominate artery pexy can sometimes exaggerate distortion of the lumen of the trachea, requiring revision of the pexy. Persistent obstruction of the trachea may also be seen because of buckled and distorted tracheal rings, which require tracheal resection, as occurred in four of our patients.

Stenosis involving less than 50% of the length of the trachea was treated by segmental resection in 15 patients, 7 with complete ring stenosis, 1 with an intact membranous trachea, 4 with localized severe tracheomalacia, and 1 with a polypoid hamartoma. Two patients had segmental resection when a rib cartilage graft developed recurrent granulomatous. In addition two children with bronchial stenosis had segmental bronchial resection. The age at operation ranged from 17 days to 3.5 years.

Anastomotic stricture developed in three infants who were all less than 23 weeks old. In two patients there was complete tracheal ring stenosis and the other had tracheomalacia associated with a double aortic arch. Resection of the stricture was accomplished in all three infants, resulting in a widely patent airway in two. In one infant (patient 13), there was recurrence of the stricture. This patient had residual stenotic complete rings the entire length of the trachea, and probably he should have had a rib cartilage graft rather than a segmental resection.

Maeda and Grillo¹⁶ showed that transection followed by anastomosis of the trachea of puppies resulted in impaired growth when the dogs were killed at 7 months of age. The anastomosis assumed a round shape instead of an elliptical one. The anastomosis grew 82% of normal sagittally and 75% coronally, with an overall lumen size 80% of normal. Symptoms of airway narrowing do not occur until the lumen becomes 50% of normal. Long-term follow-up of our patients will be required to determine if they will develop significant stenosis in later years. So far none have had symptoms or signs of airway narrowing, with up to 23 years of follow-up in one patient.

Stricture of the anastomosis might be expected because of the very small tracheal lumen present in our patients and because of tension on the anastomosis. Maeda and Grillo¹⁷ have shown that stricture occurs in puppies with only 58% of the tension, which produces stricture in adult dogs. The suture tends to pull through the soft cartilage rings of puppies, resulting in separation of the anastomosis, which is bridged by scar and subsequent stenosis. Fearon and Whalen¹⁸ measured the length of the airway from the vocal cords to the carina at the time of bronchoscopy in living infants. They obtained measurements of 5.0 to 7.5 cm during the first 3 months of life, and a range in length of 5.0 to 9.0 cm between 6 months and 1 year of age. They tried to perform the measurements with the head and neck in a neutral position, but extension of the head might readily stretch the trachea to a longer measurement than the neutral position. To use this data, one might subtract at least 1 cm to account for the distance between the vocal cords and the trachea. The normal trachea consists of 17.01 ± 1.28 cartilage rings.¹⁹ We have resected 1.0 to 2.5 cm in infants younger than 1 year and a 2-year-old patient had a 4-cm-long resection. These lengths would represent 21% to at least 50% of the normal tracheal length. However a number of these infants had an abnormally long trachea, and therefore we could overestimate the proportional length of resection. One of our infants (patient 10) had a 9-ring, 2.5-cm length of trachea resected, and his stricture was clearly due to disruption of the anastomosis by bridging scar between the separated tracheal rings. After repeated dilatation of the stricture during a 3.5-month interval, the stenosis was resected without further stricture formation. From this experience,

we believe that at least 40% of the length of an infant trachea can be resected with little risk of significant stricture, but resection in excess of 50% will probably result in progressive disruption of the suture line and a re-resection will be necessary at a later date. This experience compares favorably with Grillo's series in adults, in which 50% of trachea can be resected safely.²⁰

The choice of suture material is important. We used polyester, nylon, polypropylene, and polydioxanone (PDS). The braided polyester suture probably was responsible for an exaggerated fibroblastic healing response in one infant (patient 13). Nonabsorbable suture, such as nylon, tends to erode and produce granulation tissue in the lumen. In several of these patients, we had to remove the suture bronchoscopically. We favor 4-0 and 5-0 polydioxanone (PDS) (Ethicon, Inc.), which seems to produce minimal inflammatory and fibrotic reaction, and it resorbs.

Elongated stenosis with complete tracheal rings was treated in two infants by incising the entire length of the anterior tracheal wall and by placing a wedge-shaped cartilage graft to enlarge the airway. Cotton et al.²¹ popularized rib cartilage grafts for the management of subglottic stenosis. The use of the rib cartilage graft for intrathoracic tracheal stenosis was reported by Kimura et al.⁴ in five cases and it has been used by Saad and Falla⁵ in three patients.⁶ Campbell and Lilly²² used the rib cartilage graft in one 4.5-month-old infant with agenesis of the right lung. Our patients were 4 months and 15 months old, respectively, when operated on. In both infants, the entire trachea had a diameter of less than 5 mm, which narrowed to 3.6 mm proximal to the bifurcation of the upper and lower lobe bronchi. The 5-mm-wide rib cartilage wedge graft probably expanded the tracheal diameter at the proximal end to 6.5 mm and distally to 5.2 mm. This means that about 24% of the proximal circumference and 33% of the distal circumference must be resurfaced by respiratory epithelium from the adjacent airway (circumference = $\pi \times$ diameter) (Fig. 2). In both infants the distal portion of the wedge graft developed exuberant granulation and would not epithelialize, while the proximal tracheal graft epithelialized very well. Two patients with tracheomalacia and a normal circumference of trachea had a rib cartilage graft that represented less than 25% of the circumference, and the graft epithelialized normally. It seems that when the rib graft amounts to 30% or more of the circumference of the airway, exuberant granulation forms and resurfacing from adjacent epithelium may not occur. In the two children with recurrent granulation, the distal trachea was resected 4 and 7 months later, a length of 2.5 and 4.0 cm, respectively, with anastomosis. This has resulted in a widely patent and normally growing airway. The rib cartilage in both instances had resorbed, with a fibrous membrane remaining (Fig. 2).

One child had a pericardial patch graft to the anterior wall of the trachea after segmental resection of the middle one third. This proved to be unsatisfactory because he required prolonged endotracheal ventilatory support, and although the graft readily epithelialized, it contracted and required repeated dilatation. Idriss et al.²³ reported on five patients in whom pericardial patch tracheoplasty was used for tracheal stenosis, but granulation and contraction stenosis required bronchoscopic removal of granulations and dilatation in two of their patients. Two of their children required a tracheostomy, one because of intractable aortic vessel compression, and the other because of residual inflammatory stenosis. These authors sutured the pericardial patch to the posterior wall of the aorta and an anterior aortopexy was used to hold the airway open. In two patients they were able to extubate the patient 1 week after operation.

Filler et al.²⁴ have used periosteum from the anterior tibia with the osteogenic surface facing the tracheal lumen in five patients. None of these were satisfactory because of bony overgrowth encroaching the lumen. Other techniques to expand the lumen of the trachea include the anterior wall of the esophagus, myoperiosteal pedicle grafts from ribs, dura and dermal grafts, plus many foreign materials.^{2,24}

We favor the rib cartilage wedge graft because it is rigid, it holds suture material well without air leak, and it does not stricture. The patient can be extubated immediately after operation, and there has been no problem with retained secretions. However, if the stenosis involves less than one half of the length of the trachea, with a normal lumen beyond the stenosis, we prefer segmental tracheal resection.

Tracheomalacia may be a life-threatening problem. When it is a localized lesion, such as associated with double aortic arch, segmental resection is effective. Involvement of a long length of the trachea may be resolved by aortopexy in many patients, but in some the aorta and innominate vessels are immediately adjacent to the sternum and aortopexy will fail to put traction on the trachea. We used an external rib strut in two cases, which worked well in one and failed in another infant.¹⁰ In two patients with severe tracheomalacia, we tried to stiffen the trachea by using a wedge-shaped cartilage graft. This worked very well in one patient who had a normal width of membranous trachea. However, in another infant, in whom the membranous trachea was abnormally wide and prolapsed into the lumen, the cartilage graft provided no benefit. Greenholz et al.²⁵ describe their experience with 41 cases of tracheomalacia; in 19 cases an aortopexy was performed and 6 patients did not improve. They describe performing a tracheal resection in one of their patients and suggest that this procedure should be considered in preference to tracheostomy; particularly for localized distal tracheo-

malacia. Vinograd et al.²⁶ devised a Marlex mesh coated with silastic, which is sutured around the malacic portion of the tracheal or bronchi, to hold open the collapsing airway. Eight patients were reported with promising results. Two of our patients who had esophageal atresia seemed to develop progressive tracheomalacia and bronchomalacia. They required tracheostomy to administer continuous positive airway pressure to hold their airways open until the malacia resolved—in one child 2 years later. Better methods must be developed to treat extensive tracheobronchial malacia associated with wide tracheal membranes.

Note Added in Proof

Subsequent to this presentation, patient 17 required a rib cartilage graft because the trachea failed to grow proportionate to his somatic growth. He developed severe shortness of breath, dyspnea, and cyanosis with the slightest exercise. Following rib cartilage graft involving 14 tracheal rings, he has a good airway.

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DISCUSSION

DR. M. J. JURKIEWICZ (Atlanta, Georgia): I am very interested in the fate of the cartilaginous graft. I note that in the illustration no vascularized tissue was placed over the graft. I am making the assumption that you are using some tissue from somewhere to accomplish this.

If not, then I am wondering if a vascularized graft in the nature of a flap would be preferable to in some way enhance the circulation within the graft.

Second, what is the fate of that graft? Does it grow with the child or exactly what happens?

DR. JAMES A. O'NEILL, JR. (Philadelphia, Pennsylvania): I have two questions. Would you comment a little further on the matter of granulations? We, too, have abandoned sutures such as Prolene, and we attempt to place sutures in such a fashion that none of it would appear on the mucosal surface of the anastomosis within the trachea. Nonetheless, even with the use of long-term absorbable suture material such as Maxon or Vicryl, we still have had occasional problems with granulation tissue, and in many instances we think that this is because these patients have been infected from partial tracheobronchial obstruction.

The second question relates to something you did not allude to. Whereas we had previously felt that we could always do such reconstructions without cardiopulmonary bypass, and that is still true of short obstructions, we have found it, or at least have considered it, easier to use cardiopulmonary bypass as an adjunct in the performance of these procedures. How do you feel about this?

DR. HOWARD FILSTON (Durham, North Carolina): To put this series in perspective, in most of the latest issues of texts that relate to this subject, this lesion is still categorized as an almost overwhelmingly fatal one. Therefore this series is a tremendous accomplishment.

In using pericardial tissue, do you suspend it in the way of an aortopexy to try to give it more stability?

DR. ALFRED A. DE LORIMIER (Closing discussion): Let me show you a microscopic slide of the trachea from one of the patients who had a rib cartilage graft for complete tracheal rings. Subsequently this patient

required a partial tracheal resection because of recurrent granulations. You will note that there is only a small remnant of the rib graft, and it is not viable. The area of the trachea that was grafted with cartilage has become a membranous portion of the trachea. You will also note that the grafted area actually makes up for at least 30% of the circumference of the trachea. In addition, there has been migration of the glands normally seen in the submucosa, which have moved right across into the grafted area. There is no epithelial lining in this section of the trachea, which I think is due to using the Nd:YAG laser. The use of lasers to treat granulation tissue in the small space of a bronchus or a stenotic trachea may transmit a sufficient amount of heat to destroy the surrounding normal epithelial lining in this area.

Obviously, these grafts are not vascularized. We have relied on the thymus gland adjacent to the grafted area for protection. The use of a nonvascularized free graft is probably not a bad solution for this particular problem. Although it necroses, it is replaced by a membranous portion of the trachea that is anterior in position.

Experimentally and in some clinical situations where the rib grafts have been used to replace subglottic stenosis, many workers have reported that the cartilage remains viable, and therefore a complete cartilage ring persists.

Now about the granulation tissue, we agree that the suture should not penetrate the lumen. We try to avoid that. However, it may not be a critical issue when using the PDS suture, because it is resorbed, and therefore an ongoing granulation reaction may not occur. When we used nylon or some other nonabsorbable sutures, they were a source of granulation tissue and stricture. We have had to repeatedly bronchoscope these patients and pull the nylon out at a later stage. Therefore, we advocate the use of PDS suture as the least reactive because of its resorption.

In one patient, we used the cardiopulmonary bypass, and this was a patient with an especially elongated trachea. We felt that we needed to enhance the airflow not only by using a pericardial patch graft, but also to perform a partial tracheal resection to shorten it. Theoretically, the cardiopulmonary bypass should have allowed us to extensively mobilize the pulmonary hilum. However, that maneuver failed. We did not gain sufficient mobility to perform a very extensive tracheal resection. Furthermore, we found that there are more tubes to deal with than a single endotracheal tube used to ventilate the lung. We have had no difficulty ventilating the airway directly and therefore have not felt the need for cardiopulmonary bypass.

Hepatic Resection for Disseminated Germ Cell Carcinoma

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Improvements in operative technique and perioperative management have expanded the application of hepatic resection for metastatic cancer. Although a policy of aggressive surgical resection of residual pulmonary and retroperitoneal disease following chemotherapy and normalization of serum tumor markers has been adopted for disseminated germ cell carcinoma, resection of residual hepatic disease in these cases has not been addressed. This report concerns a series of prospectively randomized patients who received systemic cisplatin-based chemotherapy for testis cancer during the past 13 years. Twenty-eight patients underwent resection of residual hepatic disease after serologic remission. Most (23 of 28 patients) of these procedures were preformed concomitantly with other cytoreductive procedures. There were no operative deaths, although 28% of the patients developed complications. The 2-year survival rate was 54%, with an average follow-up of 34 months. Patients were stratified into three groups based on the most aggressive histology noted in the resected specimen. Survival is predicted by this histologic classification system. Hepatic resection can be performed safely and is an important component in the treatment of disseminated testicular carcinoma.

TESTICULAR CARCINOMA REPRESENTS the model of a curable solid neoplasm.¹ Before 1970 metastatic disease was always fatal. The introduction of platinum-based combination chemotherapy² has resulted in a cure rate of 95% for patients presenting with early stage lesions and 80% for those with advanced disease.³ As the recent therapy for this tumor has evolved, the role of the surgeon has been redefined.

In the preplatinum era, orchiectomy with retroperitoneal lymph node dissection was the standard therapy for nonseminomatous testis tumors. Patients with disease extending beyond the retroperitoneum were considered incurable and retroperitoneal dissection was withheld.⁴ With the advent of effective chemotherapy, reliable tumor markers, and accurate noninvasive diagnostic modalities, surgical therapy assumed an adjunctive role. After chemotherapy resection of residual disease may convert pa-

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tients considered partial responders to chemotherapy to complete responders. The development of effective post-resectional chemotherapy^{5,6} further emphasized the importance of surgical intervention as a diagnostic and therapeutic modality.

In 1980 Mandelbaum et al.⁷ expanded the indications for surgical resection for testis tumors to those patients with advanced disease. They showed that resection of pulmonary metastases could be safely performed, with or without other cytoreductive procedures, resulting in an improved disease-free survival and a more accurate assessment of the patient's disease status.⁸ Despite these early contributions, the management of residual hepatic disease has not been addressed. We believe that the principles used in the therapy of pulmonary metastases can also be applied to hepatic lesions. The purpose of this study was to review our experience with hepatic resection of metastatic germ cell carcinoma, focusing specifically on issues of efficacy and safety.

Materials and Methods

Patient Population

Between April 1976 and April 1989, 28 patients underwent hepatic resection for metastatic testicular carcinoma at Indiana University Medical Center. Fifty-four per cent (15 of 28 patients) of the procedures were performed during the last 5 years. The patients' ages ranged from 12 to 35 years, with a mean and median age of 24 years. All were white. A diagnosis of germ cell carcinoma was established before operation (Table 1). All patients presented with advanced disease (stage BIII or C).

Treatment Protocol

The current protocol for the treatment of patients with testicular carcinoma was pioneered at Indiana University Medical Center by Einhorn and Donohue.⁹ Treatment is

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TABLE 1. *Index Tumors*

Pathology	Patients
Embryonal carcinoma	11
Choriocarcinoma	3
Teratocarcinoma	4
Mixed elements	10
Total	28

based on the clinical stage of the disease.¹⁰ All patients with advanced disease received induction chemotherapy including (1) cisplatin, vinblastine, and bleomycin (n = 11); (2) cisplatin, etoposide, and bleomycin (n = 14); or (3) cisplatin, vinblastine, bleomycin, and doxorubicin (n = 3). Patients received no more than four cycles of this therapy.

After induction chemotherapy, if the serum tumor markers, beta-human chorionic gonadotrophin (HCG), and alpha-fetoprotein (AFP) normalized and there was radiographic evidence of complete tumor regression (CR), the patient was observed. If residual lesions were noted on x-ray in the presence of normal serum markers, the patient was considered to have a partial response (PR), and the residual disease was resected when anatomically possible. If active disease was encountered, postoperative chemotherapy was instituted. If the disease progressed after induction therapy, surgery was delayed and salvage chemotherapy (using an agent not previously used) was initiated. Patients with CR undergo monthly chest x-ray, HCG, and AFP determinations for 1 year. The same follow-up studies are done at 2-month intervals the following year and thereafter at 6- to 12-month intervals.¹ Patients with PR are candidates for resectional therapy.

Results

Preoperative assessment included re-evaluation of the serum HCG and AFP, as well as a repeat computed tomographic scan (CT) of the abdomen and chest. All but one of our patients had normal serum tumor markers. This patient failed salvage chemotherapy and surgical therapy was offered as a last effort to eradicate the tumor. Twenty-six of our patients underwent CT scan. A single patient, thought to have CR, was found to have multiple superficial lesions at laparotomy. The appearance of the disease on CT scan varied from isolated solid tumors to complex cystic lesions and did not predict the final pathology of the resected specimen.

The choice of operative procedure (Table 2) was based on the extent of parenchymal involvement and proximity of the tumor to the intrahepatic vessels. Bilobar lesions were noted in nine patients and isolated right or left lobe disease was found in 16 and three patients, respectively. Solitary lesions were present in 10 patients. A tumor-free surgical margin of 1 cm was obtained whenever possible.

TABLE 2. *Hepatic Operations*

Procedure	Number
Wedge resection	20
Segmentectomy	4
Lobectomy	3
Trisegmentectomy	1

Concomitant cytoreductive procedures were performed in 23 patients. These included retroperitoneal lymph node dissection (n = 17), retroperitoneal lymph node dissection plus pulmonary resection (n = 6), nephrectomy (n = 4), inferior vena caval resection (n = 4), and orchiectomy (n = 7). Three of the patients underwent staged procedures.

A total of 14 postoperative complications occurred in eight patients (Table 3). Only two of these, both biliary leaks, were directly related to the hepatic resection. Five abscesses, four subdiaphragmatic and one retroperitoneal, were noted. Six of the eight patients experiencing complication had undergone concomitant procedures. There were no episodes of respiratory failure despite the previous exposure to bleomycin.

The patients can be stratified into one of three groups based on the most aggressive pathology noted in the resected specimen. These include group I, patients with fibrotic or necrotic masses (n = 4); group II, patients with residual teratoma (n = 10); and group III, patients with residual carcinoma (n = 14). All of the group I patients are alive with no evidence of disease (NED) at an average follow-up of 31 months. Of the group II patients, nine are alive and NED with an average follow-up of 49 months. The single death in this group occurred 61 months after operation from sarcomatous degeneration of a recurrent teratoma. The average survival time in the group III patients was 23 weeks. There are only two group III survivors alive with NED at 17 and 44 months follow-up. Neither of these patients received postoperative chemotherapy. Of the 12 patients who died, five received some form of chemotherapy. The overall 2-year disease-free survival rate is 54%.

There were no perioperative deaths and the patients required an average of 2 days in the intensive care unit.

TABLE 3. *Postoperative Complications*

Complication	Number
Abscess	5
Bile leak	2
Pneumonia	2
Small bowel obstruction	1
Dehiscence	1
Chylous ascites	1
Pneumothorax	1
Thrombophlebitis	1
Total	14

Discussion

Before 1973 metastatic testicular carcinoma was reported to have an extremely poor prognosis, with mortality rates of 80% to 90%.¹¹ The advent of platinum-based combination chemotherapy has resulted in dramatic improvements in survival.^{1,2,9} Nearly all patients with early-stage disease are cured. For patients with advanced lesions, a complete response to induction chemotherapy can be anticipated in 80%, although 10% will relapse. Thirty per cent of patients with disseminated disease, therefore, will be potential surgical candidates.

The precedent for resection of advanced testicular carcinoma was established a decade ago with the resection of residual pulmonary disease.^{7,8} The same principles apply to hepatic resection. The procedure must be safe and efficacious, resulting in resection of all residual tumor and identification of patients who might benefit from additional therapy.

Recent statistics for resection of hepatic metastases reflect advances in our appreciation of segmental hepatic anatomy as well as improvements in operative techniques and perioperative care. Accepted mortality rates are 5% with morbidity rates of 5–10%.^{12–14} We did not experience any operative deaths and the complication rate was acceptable.

Five of twenty-eight patients (18%) developed postoperative abscesses, which represents a threefold increase in the published rate of 6% seen after resection of primary hepatic malignancies.¹³ Possible etiologies for this problem include breaks in technique while changing operative teams, the extent of dissection, immunologic deficiencies resulting from chemotherapy, or basic differences in the underlying disease. Of interest is the fact that despite previous exposure to bleomycin and the resultant high risk of postoperative respiratory failure,¹⁵ this complication was not seen in any of our patients. We attribute this to the restriction of perioperative intravenous fluids and maintenance of low concentrations of inspired oxygen (25% to 40%). On the basis of our data, we conclude that hepatic resection of metastatic testicular carcinoma is safe.

To determine the efficacy of hepatic resection of testicular metastases, the histology of the resected specimen must be considered. The data indicate that there are three distinct histologic patterns. These include necrotic (1) tumor or fibrotic scar, (2) teratoma, or (3) residual carcinoma. The benign findings of the first group are the result of effective chemotherapy.

Teratoma varies from the mature form with well-differentiated elements to an immature histologic pattern composed of primitive neuroectoderm, endoderm, or mesodermal components. They presence of teratoma may be the result of treatment-initiated maturation of primitive

cells or reflect residual teratoma after the primitive carcinomatous components of the original tumor are destroyed by chemotherapy.¹⁶ Although these teratomatous lesions appear benign histologically, metastases will occur in 30% of the cases within 5 years and malignant degeneration of the various cell lines can occur (*i.e.*, adenocarcinoma or epidermoid carcinoma from epithelial elements).¹⁷ Furthermore there is no effective chemotherapy for the treatment of these lesions. In group III patients with residual carcinoma, the entire variety of germ cell lesions may be present. One half (14 of 28) of our patients demonstrated residual carcinoma. Long-term survival can be predicted on the basis of the most aggressive histologic pattern in the resected specimen.

While resection of teratoma and residual carcinoma is obviously beneficial, the dilemma is how to avoid hepatic resection in patients with benign disease. The serum tumor markers, HCG and AFP, are not useful in this context. False-positive diagnoses are rare. Abnormal AFP can be the result of hepatoma, pancreatic carcinoma, or tyrosinemia, among other causes, and elevated HCG is seen with carcinoma of the pancreas, stomach, or bronchus. False-negative values are reported to occur in 10% to 80% of patients with residual carcinoma.^{18–20} All but one of the patients with residual carcinoma had negative preoperative markers.

Tumor response can be monitored radiographically. If the tumor contracts or disappears, one assumes a positive response to therapy. However, if tumor contraction stops or if the tumor never responds, then one must assume that there is no response to therapy. There are no radiographic characteristics that distinguish benign and active disease.²¹ Donohue et al.²² have noted that because of the varied forms in which these tumors present, gross inspection, with or without frozen section biopsy, is ineffective in differentiating benign lesions. At an average follow-up of just more than 5 years, only 1 of 10 patients with residual teratoma had died and 2 of 14 patients with residual carcinoma continue to be followed with NED beyond 18 months. As patients with CR rarely relapse after 18 months, these patients are considered cured.¹⁸ We believe that hepatic resection, in an effort to remove residual disease, is justified.

Testicular carcinoma is a unique malignancy because effective chemotherapy is available for the treatment of persistent or refractory disease. Nichols²³ has demonstrated that if the serum tumor markers remain normal after operation, treatment with two additional courses of induction chemotherapy will result in a 67% long-term disease-free survival. Agents such as etoposide (VP-16) and ifosfamide are effective against refractory tumors and work synergistically in a platinum-based protocol.^{5,6} The availability of these agents emphasizes the importance of

hepatic resection as an important means to identify those patients who would benefit from additional therapy. Finally, as our experience with this procedure grows, we hope to detect those patients who will not respond to conventional therapy, thereby identifying a patient population for new investigational protocols.

The success achieved in the treatment of testicular carcinoma is the direct result of continuous efforts by a multidisciplinary team. The readiness to question previous work and accept new ideas has resulted in the only existing model of a curable adult neoplasm. We believe that resection of residual hepatic metastases should be adopted as an acceptable and efficacious modality of treatment in patients with metastatic testicular cancer.

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DISCUSSION

DR. SEYMOUR SCHWARTZ (Rochester, New York): I would like to point out that the work represents an important continuum of the contributions of the faculty of the University of the Indiana related to this interesting tumor, they have had a good response to chemotherapy.

The demonstrated advantages of surgical staging over the use of serum tumor markers and/or CT scanning is a very important contribution that defines whether one is dealing with a recurrent malignancy, a benign lesion, or in fact, no tumor at all.

I would like to focus on another issue, however. Those of us who are interested in the field of hepatic resection certainly welcome any added indication for resecting segments of the liver, but offer a word of caution that we should not magnify the therapeutic effects of the resection of liver tissue in these patients.

As the authors point out, the four patients in group I had no tumor, and therefore, there was no advantage to liver resection.

In the group III patients who actually had carcinomatous malignant lesions, there is only, in fact, one survivor over the accepted 18 months,

and there is little that can be gained by liver resection. I think we should appropriately focus on the group II patients in whom the chemotherapy had transformed the germ cell carcinoma into a teratoma.

As the authors point out in the discussion in their manuscript, 70% of patients who have this teratoma will survive bearing their tumor for a long time, and it could be regarded in that 70% as being essentially a benign lesion.

Most assuredly, 30% of these tumors will undergo malignant transformation. In their series are ten patients with teratomatous lesions, and one of the patients did die, so the yield from analysis of their own patients is exactly two patients who may have benefited from hepatic resection *per se*.

Based on this analysis, I have three questions. First, if the lesion can be defined by biopsy at operation, should resection be carried out on all lesions? For larger lesions is it appropriate to do a major hepatic resection unless it has been defined as being a teratoma with 30% potential for transformation to a malignant lesion? In other words, is there a case for resecting the carcinomatous lesions based on the data?

Also, is there a role for reinstituting chemotherapy in any patient who

has no serum tumor marker? The synthesis of my concern is, is it not appropriate to perform a biopsy on the patients, and focus on the teratoma patients, and place them in a protocol and determine whether we can truly ascribe a salutary effect on their hepatic resection *per se*: truly a prospective series.

DR. R. J. GOULET (Closing discussion): Your first question, Dr. Schwartz, addressed the issue of establishing a tissue diagnosis, either preoperatively or intraoperatively. If one could reliably establish a diagnosis of necrotic tumor, the need for hepatic resection in group I patients could be eliminated. Dr. John Donohue, one of our senior authors, has prospectively studied a series of patients undergoing retroperitoneal lymph node dissection for residual germ cell carcinoma following chemotherapy. He found a poor correlation between intraoperative findings, preoperative biopsies, or intraoperative biopsies with frozen sections, and the final pathology of the resected specimen. Because of the heterogeneous nature of these tumors, preoperative and intraoperative biopsies are nonspecific and do not eliminate the possibility of residual teratoma or carcinoma.

Therefore, we resect all hepatic masses following chemotherapy and marker normalization, when technically possible.

The next question addressed the issue of resection of residual teratoma in group II patients. As you know, these lesions have a low malignant potential but tend to cause local complications, as they grow and impinge on surrounding viscera. Our inability to reliably establish an early tissue diagnosis precludes expectant therapy of these lesions. In addition, malignant degeneration of residual teratoma has been reported. For these reasons, we believe that all residual teratoma should be resected.

Finally you questioned the efficacy of hepatic resection in patients with residual germ cell carcinoma. Unlike colorectal carcinomas, which require a minimum 5 years of follow-up, patients with treated germ cell carcinoma who remain disease-free for over a year have a cure rate that exceeds 95%. In our series 2 of 14 patients found to have residual carcinoma in the resected specimen are disease-free at follow-up beyond 1 year. Previously this condition was uniformly fatal. In addition, we believe that, by diagnosing residual carcinoma, we identify a group of patients requiring further treatment and investigation, with the ultimate goal of improving their overall survival.

Liver, Kidney, and Thoracic Organ Transplantation Under FK 506

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The new immunosuppressive drug FK 506 was used from the outset with low doses of prednisone to treat 120 recipients of primary liver grafts and 20 more patients undergoing liver retransplantation. The patient survival rate after 2 to 8 months in the primary liver transplantation series is 93.3%, with original graft survival of 87.5%. Of the 20 patients in the hepatic retransplant series, 17 (85%) are living. Almost all of the surviving patients have good liver function. In addition 11 hearts, 2 double lungs, and a heart-lung have been transplanted under FK 506, with survival of all 14 patients. With all of the organ systems so far tested, including the kidney (which has been reported elsewhere), rejection usually has been controlled without additional drugs and with lower average steroid doses than in the past. Nephrotoxicity has been observed, but not to an alarming degree, and there has been a notable absence of hypertension. There is a suggestion that serum cholesterol may be lowered by FK 506, but this is unproved. Although the adverse reactions of FK 506 and the immunosuppressive mechanisms resemble those of cyclosporine, our preliminary observations suggest that FK 506 may have a more advantageous therapeutic index.

THE NEW IMMUNOSUPPRESSIVE drug FK 506 was introduced clinically in February 1989 to replace cyclosporine for liver recipients who had intractable rejection or drug toxicity.^{1,2} In March 1989, it was first used as primary therapy from the time of a cadaveric kidney transplantation.¹ Between then and the beginning of February 1990, 140 liver and 36 kidney recipients had grafting procedures at the Presbyterian University and Children's Hospital of Pittsburgh under therapy with FK 506 and prednisone from the time of transplantation.^{3,4} In addition 14 patients had transplantation of the heart, lungs, or heart-lung. The use of FK 506 for multiple-organ transplantation, pancreatic islet cell transplantation, and as a device to facilitate the recent development of a separate Veterans Administration program will be reported separately.

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Methods

Liver Transplantation

The 140 patients entered into the study between July 2, 1989 and February 4, 1990 were heterogeneous in their indications for transplantation, degree of illness, and age. For analysis they were stratified into the 120 patients receiving their first liver (primary transplantation) and 20 who were receiving their second to sixth liver (retransplantation). Each main group was subdivided into adult (18 years or older) and pediatric (younger than 18 years) categories. The techniques of liver transplantation have been reviewed elsewhere.⁵

Primary Liver Transplantation (120 Cases)

There were 105 adults and 15 infants and children (Table 1) who were given a total of 132 livers. The average adult age of 45 ± 11.5 (SD) years reflected both the aging population in our region and our nondiscriminatory policy toward older candidates; 13 (10.8%) of the 105 adults were 60 years or older. Nonalcoholic and alcoholic cirrhosis accounted for two thirds of the adult indications; 9 of these patients were B-virus (HBV) carriers. The technically 'easier' cholestatic diseases, which include primary biliary cirrhosis and sclerosing cholangitis, were only 27% of the total. There was a generally high degree of illness and urgency as this was defined by the current United Network for Organ Sharing (UNOS) stratification (Table 1): status 1, at home, functioning without nursing care; status 2, at home, not working and requiring professional nursing care; status 3, hospital bound; status 4, ICU bound; UNOstat, ICU bound on life support. Only three of the adult UNOstat patients had fulminant hepatic failure. Many of the patients with chronic liver disease had gravitated to the desperate UNOstat condition over a long period while they waited for a liver to become available.

TABLE 1. *Clinical Features of Primary Liver Recipients*

Feature	Adult (≥18 years)	Pediatric (<18 years)
Number of patients	105	15
Number of transplants	116	16
Age (years)*	45 ± 11.5 (18 to 69)	4.1 ± 4.8 (0.4 to 16)
Sex (M/F)	58/47	9/6
Disease category: No. of cases (%)		
Nonalcoholic cirrhosis†	42 (40)	Biliary atresia 8 (53.3)
Alcoholic cirrhosis	26 (24.7)	Cirrhosis 4 (26.7)
Cholestatic disease	28 (26.6)	Tumor 2 (13.3)
Tumor	3 (2.9)	Fulminant failure 1 (6.7)
Fulminant failure	3 (2.9)	
Miscellaneous	3 (2.9)	
Total	105 (100)	15 (100)
UNOS score: No. of cases (%)		
2	25 (23.8)	5 (33.3)
3	39 (37.2)	5 (33.3)
4	14 (13.3)	3 (20.0)
UNOSTAT	27 (25.7)	2 (13.4)

* Thirteen patients were ≥ 60 years old; 8 were younger than 2 years old.

† Included 9 B-virus (HBV) carriers.

Biliary atresia was the native liver disease in 8 of the 15 pediatric recipients, with cirrhosis a distant second (Table 1). The youngest child was 4.5 months old. The average degree of urgency in these patients was less than in the adults.

Liver Retransplantation (20 Cases)

These 20 patients (15 adult and 5 pediatric) experienced failure of one to five previous grafts that had been in place for 2 days to 80 months under cocktail immunosuppression with cyclosporine and prednisone, with or without azathioprine and/or antilymphoid globulin (ALG) agents (Table 2). The main reasons for graft failure were chronic rejection and hepatic artery thrombosis (Table 2). Several of these patients were sent to Pittsburgh for salvage after having their first transplantation(s) at other centers.

TABLE 2. *Circumstances of Liver Retransplantation (ReTx)*

Circumstance	Adult (≥18 years)	Pediatric (<18 years)
Number of patients	15	5
Number of transplants	18	5
Age (years)	45 ± 4.5 (21 to 64)	5.6 ± 6.5 (1 to 17)
Sex (M/F)	7/8	2/3
Causes of ReTx:		
No. of cases and % ()		
Rejection	8 (53.3)	5 (100)
HA thrombosis	4 (26.7)	
Primary dysfunction	2 (13.3)	
Recurrent HBV	1 (6.7)	
Number of grafts		
2	10	4
3	4	1
6	1	
Days from		
First graft	728 ± 862 (2 to 2435)	478 ± 278 (84 to 862)
Previous graft	460 ± 594 (2 to 2421)	475 ± 251 (84 to 862)

Treatment of the 20 patients required 23 grafts because additional retransplantation became necessary in three instances.

Thoracic Organ Transplantation

Heart transplantation. Between October 8, 1989 and February 14, 1990, heart transplantations were performed in eight adults (48 to 56 years) and three children (who were 11 months, 2.5 years, and 11 years old). The indications were idiopathic cardiomyopathy (n = 5), ischemic cardiomyopathy (n = 5), and congenital heart disease (n = 1). Four of the 11 patients needed preoperative mechanical assist device support and three more required inotropic drugs. The donor for a 52-year-old woman was her 48-year-old sister (one haplotype HLA match) who died of a stroke; special permission was obtained from UNOS to permit allocation outside of the normal priority list.

Lung or heart-lung transplantation. Two men with cystic fibrosis who were 34 and 27 years old had double-lung transplantation on October 13 and November 28, 1989, respectively. A 27-year-old woman with Eisenmenger complex had a heart-lung transplantation on October 20, 1989. She had minimal residual disability from a cerebrovascular accident several years earlier, which presumably was related to polycythemia.

Kidney Transplantation

Thirty-six kidney transplantations were performed between March 27, 1989 and January 4, 1990 and have been reported elsewhere.⁴ More than two thirds of these patients were not conventional kidney transplant recipients because of previous or concurrent transplantation of

the liver ($n = 10$) or heart ($n = 1$), positive cytotoxic cross-matches ($n = 9$), and other complicating factors that normally would have precluded renal transplant candidacy. Two (5.6%) of the patients died. Twenty-seven (75%) have good graft function (mean serum creatinine, 1.7 mg%) after 3 to 13 months follow-up (156 ± 52 [SD] days). In the present report, these cases were used for comparison of FK 506 doses, FK 506 plasma levels, and cholesterol concentrations with those of primary liver and thoracic organ recipients.

Immunosuppression

FK 506. Initial treatment is the same with all organ recipients and has been standardized as follows. Intravenous doses of 0.075 mg/kg infused during 4 hours are started in the operating room and repeated every 12 hours until oral intake is begun. The conversion from intravenous to oral doses of 0.15 mg/kg every 12 hours usually is overlapped for 1 day. Dose revisions are made on clinical grounds and guided by trough plasma levels of FK 506, which are measured with an enzyme immunoassay technique.⁶ Optimal 12-hour trough levels are thought to be in the 0.5 to 1.5 ng/mL range, but concentrations less than this may be adequate, and higher concentrations may be well tolerated.⁴ Most upward dose adjustments are responses to the break-through of rejection, combined with low plasma levels of FK 506. Downward dose adjustments usually are dictated by adverse drug reactions of which neurotoxicity is the most common and useful for clinical management.⁴ Major nephrotoxicity implies serious overdosage but is quickly reversible.

Later, variations from this generic approach were dictated by the nature of the graft, the quality of graft function, and kidney function in nonrenal and renal recipients. Because the principal metabolism of FK 506 is by the liver, the doses were reduced after hepatic transplantation if the initial liver graft function was substandard. Under these circumstances, downward adjustments of FK 506 dosage were correlated with liver dysfunction, declining renal function, neurotoxic side effects, and the demonstration of supratherapeutic plasma levels of FK 506. These were documented as high as 25 ng/mL. The supreme value of monitoring plasma levels of FK 506 was in the liver recipients. In liver recipients upward adjustments of FK 506 dosage from the generic regimen were rarely made perioperatively and then only if there was unequivocal evidence of rejection. Protocol liver biopsies were obtained at 2 weeks and 2 months to help guide management.

An effort was made in recipients of thoracic organs to keep the FK 506 doses as high as possible. Perioperatively renal dysfunction necessitated temporary reduction of the

intravenous doses in one half of the cases. This was most common when circulatory or pulmonary assist procedures had been in effect before operation. Later, changes in immunosuppression were based on the histologic findings in serial endomyocardial or lung biopsies and the results of bronchopulmonary lavage specimens. The initial response to a rejection was to increase the FK 506 dose if renal function was adequate. This approach permitted the double-lung recipients and the heart-lung recipient to be managed without maintenance steroids or any other adjuvant agent.

Kidney recipients were managed in the same general way as heart patients. Elevations of creatinine were evaluated with standard radiologic studies and kidney biopsies were obtained as needed to establish the differential diagnosis of rejection *versus* nephrotoxicity or ischemic injury. In such cases FK 506 doses were increased if there was evidence of rejection with little or no toxicity, or reduced if the biopsy did not show rejection.

Other drugs. All of the patients reported here, except for the lung and heart-lung recipients, also were given prednisone. In the first part of the experience, 1 g intravenous methylprednisolone was given to adults during operation, and a 5-day burst of methylprednisolone was begun at 200 mg on the first day and reduced daily in 40-mg steps. The doses were scaled down for infants and children. Beginning in late 1989, the intraoperative bolus and subsequent steroid cycle were omitted. Instead a daily dose was started of 20 methylprednisolone. Prednisone doses were reduced to 0 to 10 mg/day during the second to sixth post-transplantation weeks if there was no evidence of rejection.

Rejection episodes that were unresponsive to increasing the maintenance doses of FK 506 were treated with a single 1-g bolus of methylprednisolone or hydrocortisone in adults or with lesser quantities in children. If rejection persisted additional steroids were given, a 3- to 5-day course of 5 or 10 mg/day OKT3 was considered, and in a few cases azathioprine was added.

Tissue Matching

As would be expected with random matching, poor HLA compatibility was present with all of the extrarenal transplantations, except for the sister-to-sister heart transplantation. Efforts at matching in the renal cases were completely unsuccessful, despite considerable effort.⁴ Twelve (10%) of the 120 primary liver transplantations were performed, despite completely killing positive cytotoxic cross-matches. All but one of these recipients had a panel reactive antibody index (PRA) $\geq 40\%$. None of the thoracic transplant recipients had circulating cytotoxic antibodies.

Data Analysis

Patient and graft survival were recorded for each organ and actuarial survival was projected with Kaplan-Meier analyses. Data compilations were expressed as mean $\pm$ standard deviations (SD). Data from our recently reported FK 506-treated kidney recipients were used for comparisons of the FK 506 doses, blood levels, and cholesterol levels with those in recipients of other organs. Comparisons were made with a one-tailed student's *t* test and χ^2 test with continuity correction and were considered significant at $p < 0.05$.

For comparison of the present results with our previous liver transplantation experience, 400 consecutive primary transplant cases were studied, going back from November 8, 1988 to October 25, 1987. Then, as during the FK 506 study, all livers were preserved with University of Wisconsin (UW) solution. The historical controls had about the same adult and pediatric case representation as during the FK 506 study. Historical controls from November 1988 onward were not useful because so many of the later

TABLE 3. Causes of Retransplantation (RTx) Within 60 Days After Primary Liver Transplantation Under FK 506 Versus Historical Controls

	FK 506*	Cyclosporine	p
N (Starting)	120	400	
N (RTx)	7 (5.8%)	60 (15%)	<0.05
Reasons for RTx			
Rejection	1 (0.8%)	15 (3.8%)	—
Artery thrombosis	1 (0.8%)	9 (2.2%)	—
Primary dysfunction	5 (4.2%)	25 (6.2%)	—
Viral hepatitis	0	6 (1.5%)	—
Other	0	5 (1.3%)	—

Outcome of second transplantation: Five of the seven FK 506 patients are alive 3 to 5.5 months later. One of the patients who died received a total of three livers. The 90-day survival rate after retransplantation in the cyclosporine group was 34 of 60 patients.

* The patient and graft survival curves up to and beyond 60 days after primary transplantation are shown in Figure 1. Two more patients required retransplantation after 60 days in the FK 506 series, and both patients survived after receipt of their second graft and in one case a subsequent third graft.

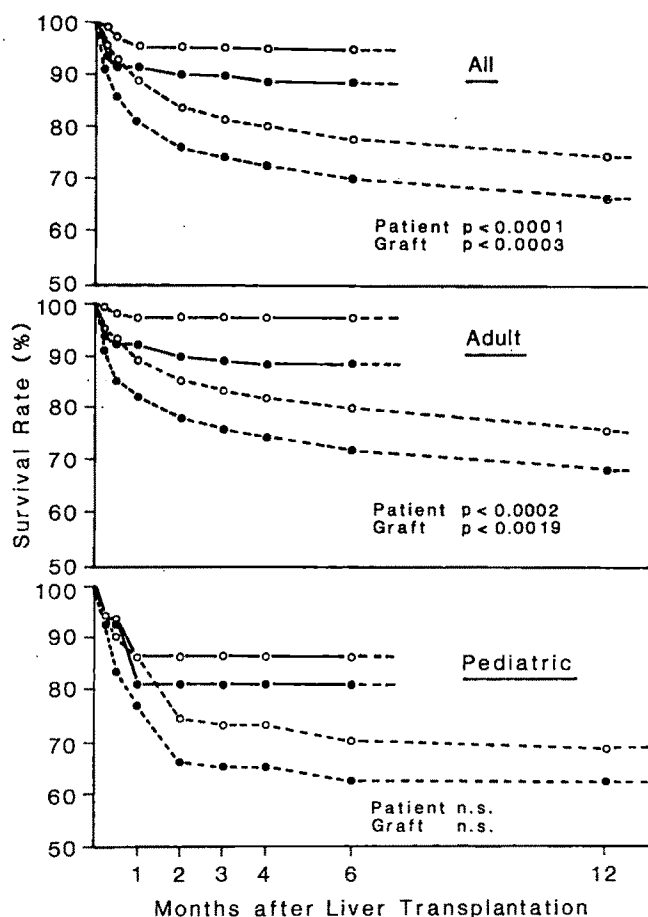


FIG. 1. Patient (O) and graft (●) survival rates in 120 cases under FK 506 therapy (—) and in 400 historical controls (---) after primary liver transplantation in all patients (upper), adults (middle), and pediatric recipients (lower).

patients eventually were switched from cyclosporine to FK 506.² In addition to patient and graft survival in all 400 cases, several other biochemical and treatment parameters were examined in smaller numbers that were determined by data availability.

Results

Primary Liver Transplantation

Patient and graft survival. One hundred twelve (93.3%) of the 120 patients are alive after 2 to 7.5 months. The patient ($p < 0.0001$) and graft ($p < 0.0003$) survival was superior to that in the historical controls (Fig. 1, top). This advantage was seen both in the adult (Fig. 1, middle) and pediatric cases (Fig. 1, bottom), although the numbers did not reach significance in the infants and children.

Rate of retransplantation. The diminished need for retransplantation at all times under FK 506 therapy is evident in Figure 1 and is documented in Table 3 for the first 60 days. Seven retransplantations (5.8%) were performed, an incidence that was almost one third of the 15% in the historical control group ($p < 0.05$). All of the usual causes of retransplantation shared in the improvement (Table 3). Also noteworthy was the absence of graft losses from viral infection.

The only FK 506-treated graft that was lost to rejection was in a highly sensitized patient who had a PRA of 100%, and completely killing positive antidonor cytotoxic cross-matches. This liver was not hyperacutely rejected (Fig. 2), but intense lymphocytic infiltration was found on biopsies 7 and 29 days after operation (Fig. 2). A second liver was transplanted after 40 days, also against positive cross-matches. This graft eventually provided normal function under intensified immunosuppression (Fig. 2)

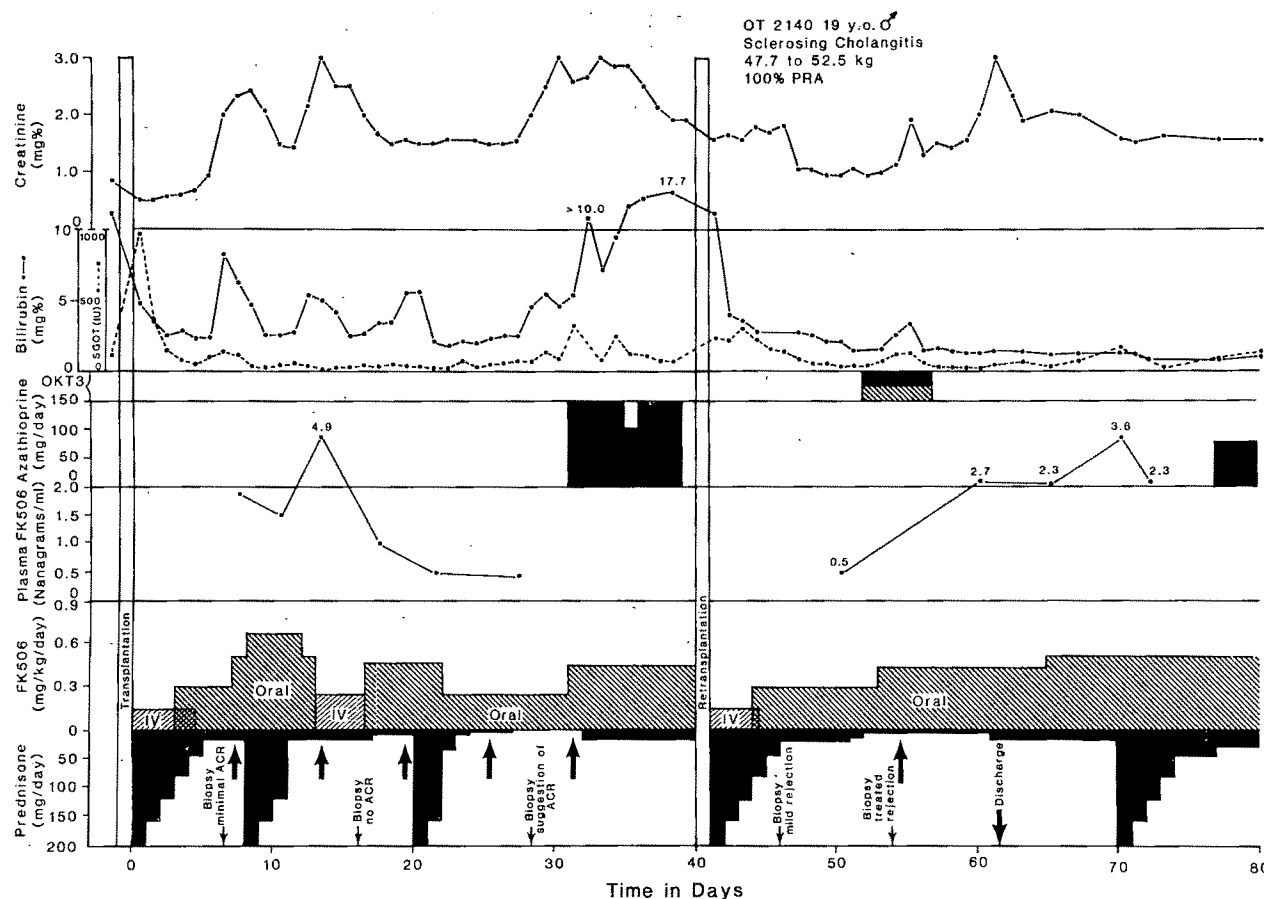


FIG. 2. Difficult course of a highly sensitized patient (PRA, 100%) who received a liver across a 100% kill cytotoxic cross-match. The therapeutic adjustments were inadequate during the rejection of the first graft. After retransplantation, increased steroids, a course of OKT3, and azathioprine were added. Eventually satisfactory function could be sustained with FK 506 and prednisone doses of 30 mg/day. The patient now is 7 months after operation and has had prednisone reduced to 5 mg/day. Note the creatinine rise, which occurred as FK 506 was increased to supernormal levels. Large upward arrows = steroid boluses. ACR, acute cellular rejection.

but at the cost of nephrotoxicity from high-dose FK 506 therapy.

It may be significant that three of the retransplantations within 60 days in the FK 506 series were in patients with strongly positive cytotoxic cross-matches. These early graft losses were from the total of 12 cases in which livers were confronted with such cross-matches. The 60-day graft loss of 25% in the cross-match-positive cases versus 3.7% (4 of 108) in the cross-match-negative cases was significant ($p < 0.05$).

Causes of death. Eight (6.7%) of the 120 primary liver recipients died within 60 days for the reasons summarized in Table 4. There have been no deaths after 60 days. The 60-day mortality rate was significantly less than in the historical controls ($p < 0.05$). Two of the deaths were after emergency retransplantation. Sepsis caused 4 of the 8 deaths. However lethal sepsis occurred at a much reduced rate compared to the historical controls ($p < 0.05$).

The fatal intraoperative complication (Table 4) was

caused by an unrecognized laceration of the subclavian artery in a 4-year-old child during anesthesia induction and placement of a central line. The patient was given only a partial first dose of FK 506 before developing an

TABLE 4. Causes of 60-day Mortality* After Primary Liver Transplantation (FK 506 Versus Historical Controls)

	FK 506	Cyclosporine	p
N (starting)	120	400	
N (deaths)	8 (6.7%)	66 (16.5%)	<0.05
Causes of death			
Sepsis	4 (3.3%)	40 (10%)	<0.05
Intraoperative	1 (0.8%)	7 (1.8%)	—
Liver failure	0 (0%)	6 (1.5%)	—
Heart failure	1 (0.8%)	4 (1%)	—
Stroke	1 (0.8%)	1 (0.2%)	—
Others	1† (0.8%)	8 (2%)	—

* There have been no deaths after 60 days in the FK 506 group. The continuing mortality in the historical controls is evident in Figure 1.

† Fulminant failure: failed to wake up.

acute hemothorax. Another child with fulminant hepatic failure did not wake up after the transplantation. Because of our policy of aggressive retransplantation, the incidence of death from hepatic failure was low in both the FK 506 and historical cases.

Liver function. One hundred twelve of the starting 120 primary liver recipients are alive, 7 after retransplantation (5 before 60 days and 2 after 60 days; Table 3). The function of the 105 grafts that have been in place continuously for 2 to 8.5 months is shown in Table 5. Only one patient with a recent biliary reconstruction has a bilirubin level more than 2 mg%. The serum glutamic oxaloacetic transaminase and alkaline phosphatase values are also normal or only slightly elevated in almost all cases.

The seven other patients who are alive after retransplantation also have generally good liver function, with only one exception.

Steroids, rejection, and adjuvant immunosuppression. Most FK 506 patients can be weaned from the prednisone rapidly during the first month (Figs. 3 and 4), leaving the FK 506 survivors on an average prednisone dose of only 6.6 mg/day at the end of this time compared to 16.7 mg in the historical controls ($p < 0.05$). Further steroid reductions were routinely made so that by 2 and 3 months the daily average doses were much less than 5 mg, significantly less than in the historical controls (Fig. 5). The appreciation of the inter-relationship between rejection and all modalities of immunosuppression during the first 30 days can be gained from Table 6. The absolute rate of clinical rejection was less ($p < 0.01$) in the FK 506-treated patients than in the historical controls, but only slightly less (NS) by histopathologic criteria. At the same time, the FK 506 patients were given only 43% of the steroid

TABLE 5. Present Metabolic Status of 105 Liver Recipients (87.5% of Original 120) Whose Primary Transplantations Were August 17, 1989 to February 4, 1990. Data from Seven Other Surviving Primary Recipients who Required Retransplantation Are Not Included (Mean $\pm$ SD).

N	
105 Days survival	128 $\pm$ 46
*105 Bilirubin (mg%)	0.8 $\pm$ 1.3
105 SGOT (IU/L)	50.3 $\pm$ 57.1
†92 Alkaline phosphatase (IU/L)	153 $\pm$ 136
†92 Serum cholesterol (mg%)	160 $\pm$ 53
95 Uric acid (mg%)	6.9 $\pm$ 4.2
105 BUN (mg%)	24.5 $\pm$ 12.3
105 Creatinine (mg%)	1.4 $\pm$ 0.7
61 Magnesium (mg%)	1.3 $\pm$ 0.3

Normal values of: cholesterol: 130 to 240 mg% (age dependent); uric acid: <8.5 mg% males, <7 mg% females; magnesium: 1.8 to 2.4 mg%.

* Only one patient with recently repaired duct obstruction has a bilirubin $\geq$ 2 mg%.

† Adults only.

SGOT, serum glutamic oxaloacetic transaminase.

BUN, blood urea nitrogen.

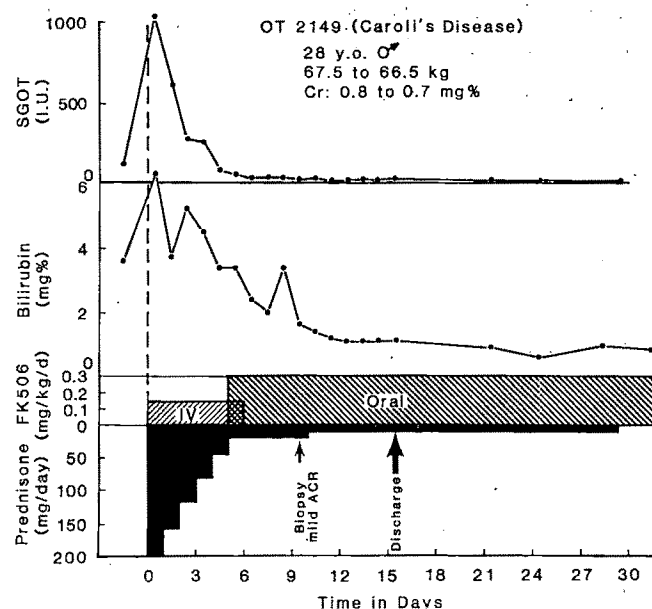


FIG. 3. Benign convalescence after liver transplantation in a 28-year-old man. The biopsy at 12 days showed mild acute cellular rejection (ACR) for which no treatment was given. He is well after 7 months. Cr = serum creatinine. SGOT, serum glutamic oxaloacetic transaminase.

boluses used in the cyclosporine controls, 7% of the 5-day steroid recycles, 4% of the azathioprine, and 23% of the OKT3 courses.

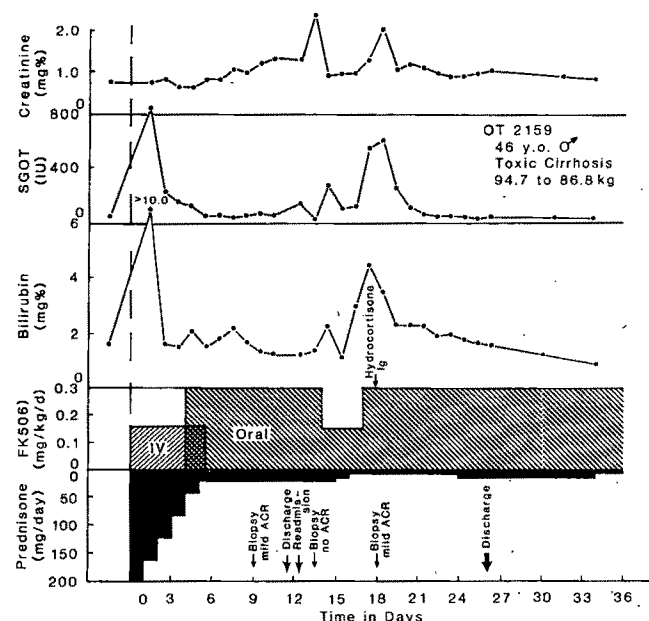


FIG. 4. Treatment of a liver rejection with a single 1-g bolus of hydrocortisone in a patient whose FK 506 was reduced temporarily because of a minor elevation of serum creatinine. After restoration of the FK 506 dose and a small increase in baseline steroids, normal function was restored. The patient is well after 7 months. ACR, acute cellular rejection. SGOT, serum glutamic oxaloacetic transaminase.

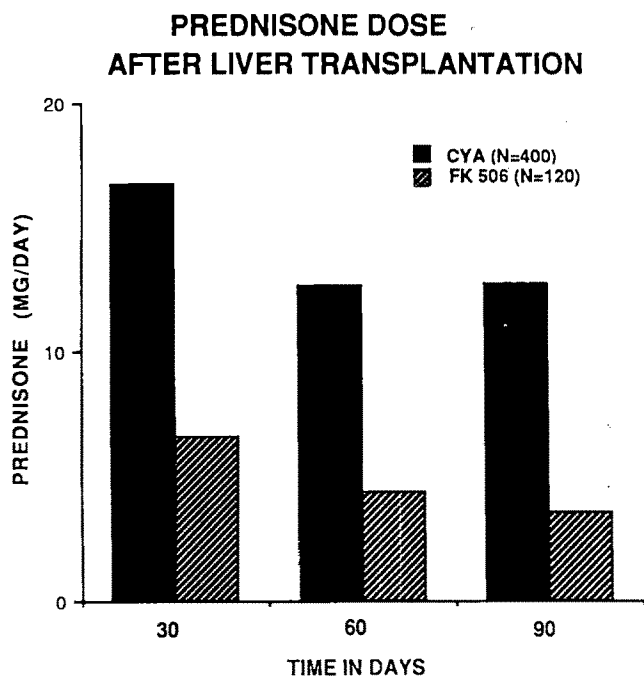


FIG. 5. Daily prednisone after 1, 2, and 3 months in the primary liver recipients treated with FK 506 versus the historical controls. CYA, cyclosporine.

The simplified management made possible by FK 506 in most patients is seen in Figures 3 and 4. Rapid recovery, early discharge from the hospital, and steroid discontinuance were possible in more than one third of the cases (Fig. 3). The patient whose course is summarized in Figure 4 had a significant rejection that was easily reversed with a single steroid bolus and an increase of the FK 506 dose.

Other metabolic tests in FK 506 patients. Present average renal function in the 105 liver recipients still bearing their original hepatic grafts is nearly normal (Table 5), as judged by serum creatinine and blood urea nitrogen. Current serum cholesterol, serum uric acid, and serum magnesium in the same patients are summarized in Table 5.

Infectious complications. The reduced incidence of fatal infections was documented in Table 4. However the patterns of nonlethal infectious disease were similar to other immunosuppressive regimens and included wound infections requiring treatment with antibiotics or surgical drainage, urinary tract infections, pneumonias, and fungal infections. The most common virus infection was cytomegalovirus. There were no protozoan infections.

Lymphoma. Polyclonal lymphoproliferative disease developed in two patients who had Epstein-Barr virus infections. A 19-year-old man had an infectious mononucleosis syndrome with enlargement of tonsils. After tracheostomy, tonsillectomy, reduction of the FK 506 dose, and treatment with acyclovir, he recovered and has no residual effects 5 months later. A 65-year-old woman

with a PRA of 100% and a positive cytotoxic cross-match rejected both her primary and a second liver, despite additional therapy with high doses of prednisone, multiple courses of OKT3, and azathioprine. She died of sepsis 9 days after a third transplantation. The second graft contained a polyclonal lymphoma with no other foci.

Adverse reactions. Two of the 120 primary liver recipients developed transient expressive aphasia 6 and 11 days after transplantation. These cases have been reported in detail.⁷ Other major neurologic complications, such as convulsions and coma, were not seen. One patient who died of cerebral hemorrhage 4 days after operation had thrombocytopenia (platelet count 10,000). Minor neurotoxic symptoms such as tremors, paresthesias, increased sensitivity to light, insomnia, and mood changes were common and were helpful in guiding dose adjustments.⁴

Ten of the one-hundred twenty primary liver recipients developed new-onset diabetes requiring insulin. If only the 112 survivors are considered, the incidence was 8.9%. The incidence of new diabetes in kidney recipients treated with cyclosporine regimens has been reported to be 10% to 20%.^{8,9}

There were no examples of hirsutism, gingival hyperplasia, or gynecomastia. A few patients noted thinning of the hair.

Liver Retransplantation

These 20 patients (15 adults and 5 children) had been under treatment that included cyclosporine and prednisone. Seventeen (85%) are alive with follow-ups of 2.3 to 9 months (Fig. 6). Two of the three patients who eventually

TABLE 6. Other Immunosuppressive Agents and Rejection in Patients Within 30 Days After Liver Transplantation

		FK	CyA	p<
N		120	303	
Steroid bolus	No	77 (64.2)	51 (18.8)	0.001
	Yes	43 (35.8)	252 (81.2)	
Steroid recycle	No	117 (97.5)	201 (66.3)	0.001
	Yes	3 (2.5)	102 (33.7)	
Immuran	No	117 (97.5)	113 (37.3)	0.001
	Yes	3 (2.5)	190 (62.7)	
OKT3	No	107 (89.2)	159 (52.5)	0.001
	Yes	13 (10.8)	144 (47.5)	
Rejection Clinical	No	73 (60.8)	138 (45.5)	0.01
	Yes	47 (39.2)	165 (54.5)	
Histopathologic*	No	51/106 (48.1)	104/248 (41.9)	NS
	Yes	55/106 (51.9)	144/248 (58.1)	

* The pathology data were not obtained under comparable circumstances. All of the adult FK 506 patients had protocol biopsies at 2 weeks and 2 months, whereas the livers in the historical control cases were sampled irregularly. A valid comparison of histopathology will require a randomized trial and protocol biopsies in both limbs.

NS, not significant.

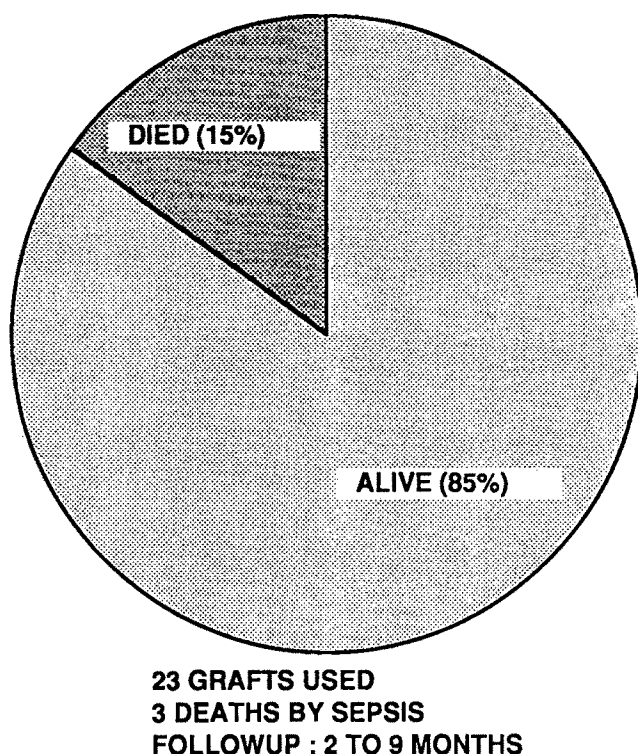


FIG. 6. Survival of patients whose previous grafts were lost under cyclosporine regimens and who underwent retransplantation with FK 506 treatment.

died of sepsis had a further attempt at retransplantation, in one patient twice, accounting for a total use of 23 grafts to treat these 20 recipients. The third death was in a child with perfect graft function who had a respiratory arrest on the ward, probably because the transplanted liver was too large for the body size.

The 17 patients who survived had more infections, a higher incidence of renal failure, and longer hospitalizations than did the patients in the primary series. However liver graft function at 30 days and subsequently was equivalent to that in the primary transplantation series.

One of the survivors was a child who underwent pancreaticoduodenectomy because of pre-existing pancreatitis that became hemorrhagic after operation. Pre-existing hirsutism and gingival hyperplasia in patients who had been on chronic cyclosporine therapy reversed in 1 to 2 months.

Transplantation of Thoracic Organs

A detailed report of these cases is scheduled for presentation to the American Society of Transplant Surgeons in June 1990 and the International Transplantation Society in August 1990. The two double-lung and the heart-lung recipients are well after 130, 165, and 173 days, respectively, never having received maintenance steroid therapy. One of the double-lung recipients has been suspected to have bronchiolitis obliterans because of biopsy findings. Because he has no complaints or deterioration of pulmonary function, other maintenance immunosuppression has not been added to FK 506.

The 11 heart recipients also are well after a mean survival time of 104 ± 54 (SD) days (51 to 180 days). One adult was treated with OKT3 and started on azathioprine as a third maintenance drug after 3 months because of histopathologic evidence of rejection. An 11-year-old child was switched by his pediatric cardiologist from FK 506 to azathioprine after 3 months, probably with insufficient reason. Other potentially important information is summarized in Table 7. The patients have been unusually free of the hypertension that was common in the historical controls. Serum creatinine concentrations were approximately the same in both groups. The serum cholesterol levels are less than in the historical controls but not significantly so.

Kidney Transplantation

Current data on the 27 kidney recipients with functioning grafts are summarized in Table 8. The low steroid

TABLE 7. Parameters in Surviving Heart Transplantation Recipients

Parameter	FK 506			Cyclosporine		
	0	30	51-90	0	30	51-90
Days						
n	11	11	11	40	36	35
Prednisone (mg/day)	—	13.6 ± 7.2	10.7 ± 8.5	—	17.8 ± 4.7	18.0 ± 4.5
Antihypertensive drugs						
One	—	0/11	1/11	—	11/36	19/35
Two	—	0/11	0/11	—	2/36	1/35
Total	—	0/11	1/11 (9%)	—	13/36 (36%)	20/35 (57%)
Serum cholesterol (mg%)		210 ± 52	220 ± 52		216 ± 41	245 ± 55
Serum creatinine (mg%)		1.1 ± 0.6	1.4 ± 0.8		1.0 ± 0.4	1.2 ± 0.5

TABLE 8. Present Metabolic Status of 27 Kidney Recipients Whose Primary Transplantations Were March 27, 1989 to January 4, 1990*

	Renal Recipients	Normal Values
Mean number of days after transplant	156 ± 52	
Creatinine (mg%)	1.75 ± 0.75	0.5–1.4
Blood urea nitrogen (mg%)	29.3 ± 13.8	5–20
Uric acid (mg%)	7.0 ± 2.3	2.5 ± 8.5
Magnesium (mg%)	1.5 ± 0.3	1.3 ± 2.1
Serum cholesterol (mg%)	176 ± 44	160–250
Patients on antihypertensives	11/28	
Daily prednisone (mg)†	4.3 ± 6.2	

* Details of all patients in this complex series are reported elsewhere.⁴

† Twenty of the 28 patients are receiving no steroids; four are on 5 mg/day.

doses, good average renal function, relative freedom from hypertension, and low serum cholesterol levels are good prognostic signs that have prompted the institution of a randomized trial in more conventional renal candidates.

Figure 7 shows a comparison of the serum cholesterol in these renal recipients with those in the liver and heart recipients. The lowest values were in the liver recipients, and the highest were in the heart recipients. The two double-lung and heart–lung recipients had very low cholesterol levels.

A similar interorgan comparison is shown in Figure 8 for FK 506 doses and plasma blood levels. Kidney recipients appeared to require higher doses to maintain plasma levels equivalent to those of the liver patients. The thoracic organ recipients were more heavily treated as a policy and had higher plasma levels.

Discussion

The accomplishments in transplantation during the last 30 years, and exponentially in the last decade, have exceeded expectations. Small steps, widely spaced in time, became large leaps with the advent of cyclosporine. Yet the nephrotoxicity and other side effects of this drug limited its value and stimulated a search for better agents. FK 506 was a product of this search. It was discovered in Japan by Kino et al.¹⁰ in 1984 during systematic screening for drugs with antimicrobial, antineoplastic, or immunosuppressive qualities.

FK 506 is a macrolide antibiotic (such as erythromycin) that is recovered from the fermentation broth of the soil fungus *Streptomyces tsukubaensis*. FK 506 has no structural similarity to cyclosporine, but it has in common the ability to inhibit the synthesis and expression of interleukin-2 and other cytokines, including gamma interferon.^{10–12} Like cyclosporine, FK 506 suppresses T-lymphocyte activation, adoptive immunity, and alloreactivity

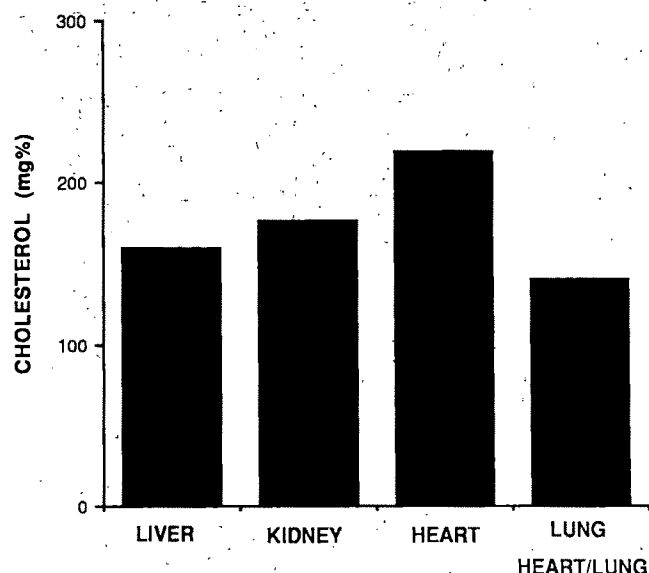


FIG. 7. Serum cholesterol comparison in recipients of different organ recipients.

(rejection) *in vitro* and in homotransplantation models. The drug can mitigate or prevent the rejection of heart, liver, kidney, pancreas, lung, intestine, and skin grafts in mice, rats, dogs, monkeys, baboons, and humans. The international exchange of this burgeoning information was facilitated by satellite symposia of the European Society of Organ Transplantation in 1987 and 1989.^{13,14} Clinical trials have been in progress in Pittsburgh since February 1989. The ultimate role of FK 506 in transplantation practice has not been fully delineated, but there are indications from our experience that it may be a large one.

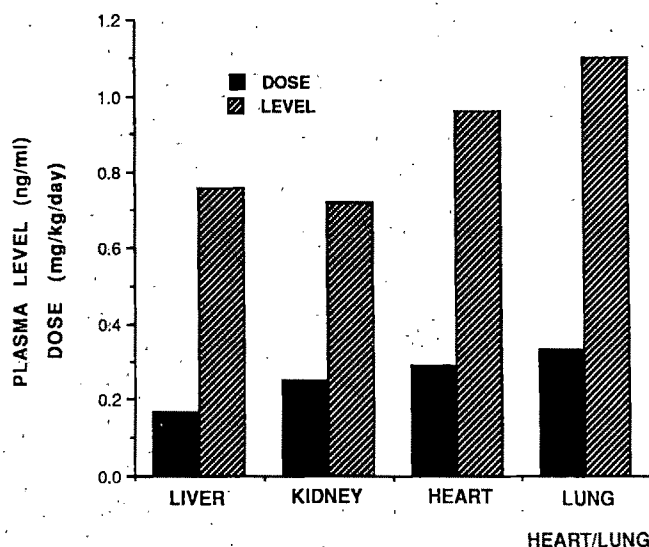


FIG. 8. Dose and plasma level of FK 506 in different organs.

FK 506 was used first clinically to treat liver recipients whose convalescence was unsatisfactory under cyclosporine-containing regimens.^{1,2} However all of the transplantations in the present report were with FK 506 therapy from the outset.³ Because of the variety of the organ grafts, specific questions could be addressed about toxicity, dose requirements, and metabolic changes that might have been less accessible with only one kind of organ graft.

With both primary hepatic transplantation and retransplantation, there were high rates of graft and recipient survival. The patients treated were thought to be of the same level of difficulty if not greater than in our past experience. Extremely ill, old, or very young patients were represented in large numbers as well as those with hepatitis B virus infections, renal failure, previous portal-systemic shunts, and multiple upper-abdominal operations.

The improvement in results with FK 506 compared to historical liver transplantation controls began with a greatly reduced need for retransplantation. A distressing statistic in most liver transplantation centers has been a 10% to 20% incidence of primary graft nonfunction (usually dysfunction), which has been explained by undetected pre-existing donor disease, poorly performed procurement, inadequate preservation, or a flawed recipient operation.¹⁵ Despite the validity of these various explanations in some cases, there has been a surprising lack of correlation between recipient outcome; the use of so-called good, mediocre, and poor donors; or the surgeon's perception of his or her technical performance.¹⁵ The low incidence of primary graft dysfunction and a reduced rate of hepatic artery thrombosis in the FK 506 patients may be indirect evidence that many early postoperative graft dysfunctions or thrombotic events are caused by immunologic factors that have not been recognized. In a few cases, there has been strong evidence that this can occur, despite a negative cytotoxic cross-match.¹⁶ In the present report, the cytotoxic cross-match was identified as a special but surmountable problem.

In addition to high survival rates after both primary liver grafting and retransplantation, the quality of liver function was generally good, reflecting excellent control of rejection. This was achieved with low steroid doses and with minimum need for the azathioprine or the ALG preparations that have been used in cyclosporine 'cocktail' regimens. There was a low incidence of nephrotoxicity in the primary recipients not previously exposed to cyclosporine and a somewhat greater incidence in the retransplantation series. The arterial hypertension that has been associated with cyclosporine therapy¹⁷ was very uncommon. Hirsutism and gingival hyperplasia were never seen in fresh cases and disappeared in retransplant recipients when they were switched from cyclosporine to FK 506.

The impression should not be left that FK 506 is free of nephrotoxicity. Nephrotoxicity is merely less than that

of cyclosporine, and seemingly more reversible. Nephrotoxicity was uncommon in the liver recipients and was not used as a barometer to establish a dose ceiling. However, in our double-lung and heart-lung recipients in whom steroids and other immunosuppressive adjuncts were avoided, FK 506 was given to the limit imposed by elevations in the serum creatinine to more than 2 mg%.

These results have given a very favorable impression of FK 506. Whether comparisons with historical controls are valid or fair remains to be determined in future randomized trials because excessive immunosuppression, particularly with prednisone, may have been given in the recent control cases. Ten years ago, when cyclosporine was first used with steroids for liver transplantation, prednisone was used sparingly and discontinued early when possible. The results were comparable to those obtained at other centers in later years.¹⁸ By the late 1980s, a worldwide drift had occurred (including at our center) toward complicated multiple-drug management for all kinds of organ transplantation in an effort to minimize cyclosporine nephrotoxicity. Kahan¹⁷ has pointed out that there have never been well-designed randomized trials to test the legitimacy of this now widely accepted practice. Instead of reflecting better immunosuppression when cyclosporine was used with multiple other drugs, much of the improvement in global results after liver transplantation could be due instead to better preservation methods, acquisition of surgeon experience, improvements in infectious disease management, and more discriminating case selection by teams striving to establish credibility. This last factor may be the most important of all in a competitive market place in which survival claims can make or break a program. How profoundly the seriousness of pre-existing disease and other risk factors, including age, can influence the outcome has been demonstrated precisely in patients with primary biliary cirrhosis.¹⁹

Whatever the merit of these reservations, the advantage of a simple FK 506-steroid management regimen appeared to be the same with other organs than the liver. For example, in the heart recipients, of whom all 11 are alive, neither permanent renal dysfunction nor serious hypertension have been observed during follow-ups of 2 to 6 months. Because cholesterol is thought to be up-regulated by cyclosporine,²⁰ particular attention was paid to serum cholesterol levels in the FK 506-treated patients. Using FK 506, cholesterol levels have been reported to be low to normal in kidney recipients,⁴ and these were even lower in the liver, the lung, or heart-lung recipients in the present report (Fig. 7). However cholesterol lowering was not evident in the 11 heart recipients of the present report, possibly because they were being given more steroids than the other organ recipients. Alternatively hypercholesterolemic patients may have been over represented in the heart group of whom five of the 11 had

coronary artery disease. If the cholesterol-lowering qualities of FK 506 can be validated with more experience, cyclosporine-related hypertension and hyperlipidemia, two of the most serious present-day risk factors for coronary artery disease in heart, kidney, or liver recipients may be ameliorated.

FK 506 has additional metabolic effects. In addition to its immunologic and other qualities, which have been discussed, it is diabetogenic to the same extent as cyclosporine, augments hepatic regeneration, and can be neurotoxic. It has become increasingly apparent that many, if not all, of the organ systems and physiologic end points affected by FK 506 are the same as for cyclosporine, although to differing degrees and sometimes in opposite directions.^{4,21} This was puzzling at first because FK 506 and cyclosporine have no structural similarities and have different cytosolic binding sites. However now it is suspected that the two drugs may act on an enzyme called *cis-trans* peptidyl-prolyl isomerase (PPIase), which is a principal constituent of the binding sites.^{22,23} PPIase, which was discovered in the pig kidney in 1984,²⁴ is widely distributed in tissues from the lowest to the most developed species, including humans. Although PPIase was known to facilitate the biologically important process of catalysis of oligopeptide bonds and to facilitate protein folding,²⁴ the physiologic significance of PPIase did not begin to come to light until its possible role in immune modulation was realized.^{22,23} We have speculated that the positive as well as adverse immunologic and other wide-ranging effects of FK 506 and cyclosporine result from alteration (probably inhibition) of the PPIase system in many tissues in ways that are not yet understood.²¹

The influence of the route of administration on these diverse effects also is being clarified by observation of patients. Because orally administered FK 506 and cyclosporine are presented in high concentration to the liver, and largely metabolized there, it has been suggested that they might be more effective in protecting liver grafts from rejection than in protecting other organs, such as the heart and kidney, which are beyond this first pass 'filter.'²⁵ No conclusions are possible about this possibility. The liver recipients have been maintained on smaller average doses of FK 506 and with lower plasma levels than recipients of kidneys or thoracic organs. The average doses have drifted down in liver recipients largely in response to minor complaints of toxicity and because higher doses did not seem necessary for control of hepatic rejection. This may have reflected physician policy rather than any fundamental biologic difference. Alternatively the difference in FK 506 dosaging with the liver *versus* the nonhepatic transplantations might be because of subtle dysfunction of transplanted livers, which would not be a comparable factor of FK 506 drug disposition in heart or kidney recipients who usually have normal native livers.

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DISCUSSION

DR. FELIX T. RAPAPORT (Long Island, New York): I want to congratulate Tom Starzl for his outstanding presentation as well as for receiving the Association's highest award for scientific achievement. When the early studies of FK 506 were first presented in 1987, it was quite clear that Tom and his group were the only ones who believed that this agent was any good or had any potential whatsoever. We see today the fruition of Tom Starzl's efforts, exhibiting that tenacious faith and boundless energy of his in developing what is clearly a new milestone in immunosuppression.

It is an irony of nature that the one species that seems to be least susceptible to the toxic effects of FK 506 is its ultimate beneficiary, the human subject.

The importance of FK actually may reach far beyond transplantation, as Tom Starzl just noted, using autoimmune disease as one example.

It is quite possible that FK may be a model probe for further study of the molecular aspects of immune responsiveness and cell function.

Along these lines, while FK seems to exert the same immunosuppressive effects as cyclosporine, I was struck, in seeing the manuscript, that Tom was kind enough to show one that there were key differences between these two agents. They have different binding sites on the lymphocyte surface; FK is a hair thinner, using cyclosporine causes hirsutism; FK has no effect on the blood pressure, and may actually even decrease serum cholesterol levels, while cyclosporine produces hypertension and hyperlipidemia. Finally, FK seems to facilitate transplantation in the face of positive cross matches for anti-HLA antibodies, albeit with a 25% failure risk.

One wonders whether this agent, therefore, could not also be of relevance to facilitate ABO-incompatible transplantation, as a potential model for xenotransplantation.

The results that Dr. Starzl lists in his manuscript suggest that it may be possible that even the most violent humoral-mediated rejection might require the participation of cell populations that can be rendered incompetent by an agent such as FK.

I would be very interested to hear Dr. Starzl's comments on this possibility.

Dr. Starzl also suggests in his manuscript that FK might exert its effect by inhibiting an enzyme, PPIase, which is a component of the receptor sites for both cyclosporine and FK. I would like to ask Dr. Starzl whether this enzyme is also a component of other major immunomodulating receptors on the lymphocyte surface, such as CD4, CD8, or DR, for example, and whether the expression of such other markers is affected in any way by FK.

My final question relates to the more profound immunosuppressive efficacy of FK. Could this be the 'missing link' in our life-long goal of inducing specific tolerance to allografts in humans?

DR. G. KLINTMALM (Dallas, Texas): I want to express my profound admiration for Dr. Starzl, not just for the work that he has presented, but also for bringing this drug from the laboratory to the clinical setting. This is truly a hallmark presentation, and I think we see here the first drug in the next generation of immunosuppressive drugs.

As indicated in the abstract, we do not see as impressive a result after kidney transplantation as with heart-lung or liver transplantation. The same has actually been reported by Dr. Starzl's group in the canine model. Do you believe there may be a first-pass effect of FK that may be responsible for this difference?

DR. OSCAR SALVATIERRA, JR. (San Francisco, California): There is no group in the United States clinically using FK currently other than the Pittsburgh group, and they are to be commended for their courage and leadership role with this new agent.

Previous reports by the Pittsburgh group describe FK in rescue of failing grafts under cyclosporine therapy. This report now describes the first use of FK as the primary immunosuppressive agent in liver, kidney, heart, heart-lung and double lung transplantation from the time of graft implantation.

The report compares the use of FK with a good historical control group of patients treated with cyclosporine, the drug that heralded the new era of improved transplant success in the 1980s.

It appears from this report, and if the findings are confirmed in future clinical trials that will soon begin at other centers, that organ transplantation may now be entering another era of success with hopefully concomitant reduced sequelae from multiple drug therapy protocols that are currently in use.

Of great interest is the early significantly improved graft and patient survival rates in liver, heart, and/or lung transplantation and decreased retransplantation rates in these groups.

The kidney group is more difficult to evaluate, in that 10 of the 36 patients had other nonrenal organ transplants and nine had positive cytotoxic cross-matches against the donor, conditions that would have generally precluded renal transplantation at many centers. Yet 75% graft survival was achieved in this complex group.

The lower incidence of rejection episodes in the FK group of patients is extremely important, as it portrays a lesser need for increased or prolonged steroid and other drug usage. In fact, rejection was in general easily and successfully treated with just one pulse steroid bolus in most patients. More importantly, most patients were off steroids or on very low steroid dosages. Off steroids were 100% of the heart-lung and lung recipients, greater than one third of the liver recipients, and 71% of the kidney recipients.

If one examines these early findings as presented, the 1990s may well witness a new and meaningful breakthrough in immunosuppressive management.

I have two questions for Dr. Starzl. Have you established immunologic and outcome criteria by which you can safely convert patients to FK monotherapy, eliminating steroids?

Second, kidney recipients appear to require higher doses of FK to maintain equivalent plasma levels, as the liver recipients presumably related to the initial pass of the drug through the liver and its metabolism by that organ. How critical and important is the careful drug dosing by plasma levels in the kidney recipient, and how reliable is the currently used assay methodology?

DR. JOEL D. COOPER (St. Louis, Missouri): As has been pointed out many times, cyclosporine really ushered in an explosion of transplant activity, but we have all been hoping for something better. Perhaps FK is that next giant leap forward.

Primarily I wanted to thank him and acknowledge his assistance with one of our patients, a woman who had a double-lung transplant and did very well for 15 months, but who then went into fulminant and unremitting rejection. With his encouragement and advice and his offer to help us with FK 506 on a compassionate basis, we replaced both her lungs. She is now out of the hospital and has done very well.

I realize that one mouse is no mouse, but certainly in this case the use of FK 506 greatly simplified the management of this patient. Dr. Starzl I owe you a piece of chocolate cake because she is a wonderful cook and brought me a chocolate cake the other day. I think I was supposed to bring you a piece, but I ate it.

DR. JOSEPH E. MURRAY (Wellesley Hills, Massachusetts): It is challenging to learn of new drugs that are improving the results of human organ transplantation. It was in 1962 at a meeting of this Association that we first described the effectiveness of immunosuppressive drugs for renal transplantation in dogs and man (Ann Surg 1962; 156:337).

The drugs used then were azathioprine and actinomycin C. The use of steroids as a supplement soon followed. Cyclosporine came onto the scene about 15 years ago, and now we have FK 506.

I've always been interested in the mechanism of action of these various drugs, so I'd like Dr. Starzl's opinion as to whether or not all drugs act differently or is there a final common pathway of action. Tom has had wide experience going back to the early days of Imuran treatment.

In our canine renal transplants in the mid 1960s we were pleased and surprised to be able to wean completely some of the long-term allografted dogs from the drugs. The same happened in an occasional patient in whom we were forced to withdraw therapy for medical reasons. Do you feel that FK506 may be able to produce a permanent tolerance? Is it easier to withdraw therapy using FK506 than with other drugs?

DR. ROBERT E. CONDON (Milwaukee, Wisconsin): I would like to ask a few questions that don't have to do with the use of this drug as an

immunosuppressant but relate to its status as a macrolide antibiotic. The first has to do with possible effects on gut motility. The macrolides stimulate gut smooth muscle in various ways. That is what accounts for the nausea that is occasionally associated with the administration of erythromycin, for example.

So my question is: In your patients, have you noted any change in bowel habits, and if so, is the change in transit time responsible for the changes that you have noted in the cholesterol levels in your patients?

The second question has to do with possible antibacterial effects of this macrolide. There was a startling improvement in the overall sepsis rate in these patients and, although most of that is probably due to the fact that they got less steroids, could it possibly be related to some direct antibacterial effect of the macrolide drug?

PROFESSOR PETER J. MORRIS (Oxford, England): I would like to ask Dr. Starzl to comment on the histology. I was very excited about 6 months ago when I saw some histology from routine biopsies in patients with liver transplants at about 2 to 3 weeks after the transplant, showing no evidence of rejection whatsoever. This was a fairly unique finding in the relatively small number of transplants done at that time.

I gather that cardiac transplants on routine biopsy do show a cellular infiltrate that looks not dissimilar from what is seen with cyclosporine. Again that was, of course, in the first half-dozen patients or so, and I would like a follow-up on that. Also, I would be interested to know if there is any information on the histology of the kidney transplants. Certainly the histologic findings in the liver transplants were absolutely dramatic and I just wonder if that is unique to the livers.

DR. THOMAS E. STARZL (Closing discussion): I particularly wanted to say hello and thank you to Dr. Murray, to tell him how pleased I am to have him hear this paper and to acknowledge the fact that the first steps toward the summit, which he took, were the most important ones. The question of tolerance induction that Felix Rapaport already discussed is a very difficult one. I think as you (Dr. Murray) yourself showed and we have emphasized over the years, the accidental achievement of tolerance, if that is what it is, probably follows the same pathway using all drugs, and so what you saw with those early Boston dogs named Connecticut and Massachusetts is probably what we can see today, and induce with FK 506 but apparently with greater predictability than at any time in the past. It is very difficult to get papers published that actually examine the mechanism of graft acceptance, because all such papers interdict the opinions or biases of most of the referees. We have such a manuscript out there at the moment, which suggests that all hypotheses up to the present are wrong. The truth is that we do not know why some grafts are accepted, and others are not.

Of all of the discussions of this morning, I was actually most intrigued and learned the most from that of Dr. Condon because he is an expert on infectious disease. If Dick Simmons is here, I hope that he heard Dr. Condon's two questions, the first being about the potential antibiotic effect of the FK. This is a fascinating suggestion, and I wish I had thought of it myself. We will follow up your idea, and if you are right, we will claim it as our own.

Concerning the second question, I think that there potentially is an effect on GI motility and GI function, although it is very hard to detect. In dogs, the GI toxicity of FK 506 was actually what scared off the Cambridge group because it made the dogs so sick that many of the animals developed intussusception. This was the toxicity that we had feared the most in our first humans, but it did not materialize.

Dr. Klintmalm, I suspect that there is a first-pass removal of FK 506 by the liver and this may make it easier to treat liver recipients who take the drug by mouth and who therefore have it presented in high concentration to the liver. Because a diminished amount leaks through, this may make it necessary for larger doses to be given for organs not exposed to the splanchnic venous return. If this is a genuine dose-adjustment phenomenon, it must also apply, although it has never been studied formally, with cyclosporine. Many of the kinetics including liver metabolism of cyclosporine and FK 506 are similar. So far, the bottom line is

that the liver recipients do require a smaller dose, as discussed in the manuscript.

Dr. Salvatierra also has asked important questions, of which the foremost is which patients can have the steroids stopped. I wish we had a foolproof formula for prediction. What we do in practice is go down to zero steroids automatically, and then if we get stung with a rejection, we resume steroids. The implications of a rejection under those circumstances are less grave than in the past, since the patients usually can be rescued rather easily from such rejections. Thus, the game is worth the candle to try steroid discontinuance at least once with the liver recipients.

To answer Peter Morris' question about the liver biopsies, there is evidence of rejection in many of the biopsies. In kidney grafts, the same is true. Drs. Jake Demetris and Barbara Banner, our pathologists, did a blind study of cyclosporine *versus* FK 506-treated kidneys. There was a conviction at one time that the vascular lesions of rejection would be more common in the FK patients. This was not the case, and in fact the findings were the other way around. The vascular lesions occurred at about one-third the rate in the FK 506 kidneys compared with the conventional cyclosporine regimen. It is difficult with blind reading to make a qualitative distinction about rejection patterns in any given case. In both kidney and liver grafts, eosinophils may be prominent with either drug. I think that this occurs when there is an effort to move downward in steroid doses.

The heart biopsies are very difficult to interpret. These biopsies tend to guide therapy, since there is not a biochemical litmus paper as we have with the other organs. The dependence on cardiac graft biopsies is very nearly complete, but whether or not those cells that are being found in the endomyocardial biopsies should actually trigger responses in therapy is an open question. What we are doing in many of our patients whose grafts do have these cells, is to make minimal and sometimes no therapeutic adjustment if the patients are well clinically.

Felix Rapaport and some one else also asked, what can be done with FK 506? Can it play a role in research in heterotransplantation? That, of course, is the next step, and I think the answer is yes, but. The 'but' is that something has to be done about the heterospecific preformed antibodies that are present with cross-species grafting. Twenty-seven years ago, we showed how close to possible it was even then to transplant baboon kidneys to humans. I believe that the cell-mediated rejections that occurred with those baboon-to-human transplantations could be controlled with the drugs we have today, but what we can not control are the humoral rejections. So, Felix, I think that this is the component of the problem that we must work on. We are advising against such trials, at least at the moment.

I see that the warning light is blinking that precludes my answering the most important question of all about the peptidyl-prolyl isomerase (PPIase) enzyme system. This enzyme is contained in the binding sites of both cyclosporine (cyclophilin) and FK 506 (binding site not yet named). These are distinct binding sites, and yet they have as their principal constituent the PPIase, which was discovered 5 years ago. PPIase had no known function until about a year ago, when it was recognized to be the principal constituent of cyclophilin. Now it is assumed that inhibition of PPIase is central to the action of both FK 506 and cyclosporine, even though FK 506 has no biochemical relationship to cyclosporine. What has happened here is that by accident a novel new class of cytosolic proteins (binding sites) has been discovered that is involved across a broad range of signal transduction processes that control the interior chemistry of the cell, not limited to immune modulation. This has been evident by studying the effects of the two PPIase inhibitors (cyclosporine and FK 506) on numerous physiologic processes, including carbohydrate, cholesterol, and uric acid metabolism; control of liver regeneration (both drugs augment this process), neurologic functions, and hair growth, to supply an incomplete list.

Finally, I want to pay tribute to Joel Cooper, the courageous Washington University surgeon who earlier today gave a classic paper on lung transplantation. The case he mentioned in discussing our paper is the first successful double lung retransplantation of which I am aware. It must have been a technical *tour de force*, and we were proud to help him from a distance.

The Role of Graft-derived Dendritic Leukocytes in the Rejection of Vascularized Organ Allografts

Recent Findings on the Migration and Function of Dendritic Leukocytes After Transplantation

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Dendritic cells isolated from lymphoid tissues are potent stimulators of primary allogeneic T-cell responses *in vitro* and *in vivo*. Similar major histocompatibility complex class II-bearing dendritic-shaped leukocytes are contained within transplanted organs and these are thought to be important passenger leukocytes that trigger rejection. Recent findings on the migration, phenotype, and function of cardiac dendritic leukocytes (DLs) are reviewed. After transplantation donor DLs migrate rapidly from mouse cardiac allografts into the recipients' spleens. Within the spleens donor DLs associate with recipient CD4⁺ T cells. Isolated cardiac DLs, like lymphoid dendritic cells, are potent stimulators of T-cell proliferation *in vitro*. This suggests that DLs function as passenger leukocytes by migrating from grafts into the lymphoid tissues of the recipient and that sensitization to vascularized organ allografts may occur centrally within lymphoid tissues rather than peripherally in the graft itself.

DESPITE THE ADVENT of potent immunosuppressive drugs such as cyclosporine, allograft rejection still remains a major source of morbidity and graft loss in the modern era of organ transplantation. This is particularly true in the early post-transplant period. For instance in 1989, 64% of patients receiving a cadaveric renal allograft in Oxford experienced at least one episode of acute rejection. Of these 82% occurred within the 21 days after transplantation. Future advances in transplantation will depend on an improved understanding of the mechanisms involved in allograft rejection, which will in time allow the interruption of this process in more selective ways.

The process of rejection is generally divided into the afferent or sensitization phase, defined as the initial activation of the recipient's T cells against graft antigens,

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and the efferent or effector phase, the process of graft damage and destruction. Knowledge of the effector mechanisms that could potentially be involved in allograft rejection has improved considerably in recent years (reviewed in Mason and Morris¹). For example alloreactive cytotoxic T cells and the means by which they damage their targets (such as TNF- β and perforin), and the function of various cytokines produced by T-helper cells have been characterized. In addition anti-human lymphocyte antigen (HLA) antibodies are known to be important mediators of antibody-mediated hyperacute rejection. Also we are beginning to understand more about the cellular mechanisms leading to the initiation of rejection and an important role for dendritic leukocytes has been suggested by *in vitro* studies.

A considerable amount of direct and indirect evidence suggests that dendritic leukocytes contained within transplanted tissues are important 'passenger leukocytes' that trigger rejection (reviewed in Austyn and Steinman²). In certain experimental models it has been found that removal of leukocytes³⁻⁶ or specifically the dendritic leukocytes (DLs)^{7,8} from allografts before transplantation can lead to prolonged or even indefinite graft survival in the absence of immunosuppression, although this has not been a universal finding.⁹ Furthermore it has been shown that donor lymphoid dendritic cells (DCs), but not B cells, macrophages, or T cells, could cause rejection of a stable graft.^{7,10}

This communication provides an overview of current concepts of DL, reviews our recent findings on DL migration in murine transplant models,^{11,12} and provides an update of our ongoing investigations on the phenotype and function of these potent immunostimulatory cells.

Characteristics of the Dendritic Leukocyte Lineage

Dendritic cells were originally isolated from lymphoid tissues of rodents and later humans and were shown to

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TABLE 1. *Distribution of Dendritic Leukocytes*

Type	Localization
Lymphoid dendritic cells	Cells isolated from lymphoid tissues and studied in vitro
Interdigitating cells	T-cell areas of secondary lymphoid tissues, spleen and lymph nodes, and medulla of thymus
Veiled cells	Afferent lymphatics
Langerhans cells	Epidermis of skin
Nonlymphoid or interstitial dendritic leukocytes	Epithelial surfaces (gastrointestinal, biliary, urogenital, respiratory), and interstitial connective tissues of most nonlymphoid organs (heart, thyroid, pancreatic islets, etc.)

have a characteristic phenotype, distinct from other cell types (Table 1).^{13,14} Similar dendritic-shaped leukocytes expressing high levels of major histocompatibility complex (MHC) class II molecules were subsequently found in most nonlymphoid tissues in the body and were presumed to be related to the lymphoid dendritic cell (Table 1).¹⁵ There are, however, important phenotypic and functional differences between the cells in the periphery and those in the lymphoid tissues (Table 2)^{16,17}; see also Langerhans Cells section). We now use the term dendritic leukocytes to encompass the entire lineage and reserve the term lymphoid dendritic cells for cells isolated from lymphoid tissues. The most extensively studied nonlymphoid DLs are the Langerhans cells (LC) of skin, although it is becoming increasingly clear that the DLs in heart, kidney, mesentery, pancreas, and biliary and urogenital epithelium are phenotypically more similar to LCs than to lymphoid DCs (Roake JA, Larsen CP, Leow K, and Austyn JM, unpublished observations).

While the marrow stem cells that give rise to DLs have not yet been defined, lymphoid DCs have important functional properties that distinguish them from other

leukocytes. Most importantly, they have the ability to activate resting T cells (immunostimulation). Whereas a wide variety of other cell types can present antigens to activated T cells (which include T-cell clones), DCs are the principal activators of primary (resting) T-cell responses, such as the activation of naive allogeneic T cells in mixed leukocyte reactions.^{18,19} In contrast most evidence indicates that allogeneic macrophages and resting B cells,^{18,19} as well as endothelial cells, cannot activate naive allogeneic T cells (Patel D, Nuffield Department of Surgery, manuscript in preparation). The way in which DCs activate T cells is not known, but almost certainly IL-1 is not required because neither DC from mouse spleen nor human tonsil can synthesize IL-1.^{20,21}

In contrast to lymphoid DCs, freshly isolated LCs are only weak stimulators of resting T-cell responses, although they can process antigens. Langerhans cells can, however, mature into potent immunostimulatory cells that are virtually indistinguishable from lymphoid DCs after culture in the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF).²² At the same time that LCs acquire immunostimulatory properties, they lose their antigen-processing capability¹⁷ (Table 3). This cytokine is produced by a wide variety of cell types in various tissues.^{23,24} If the DLs of other nonlymphoid tissues have similar properties to LC, then GM-CSF production may play an important role in promoting maturation of resident DLs contained in transplanted organs into potent immunostimulatory DCs that can activate the recipient's immune response.

Migration Properties of Dendritic Leukocytes in Normal and Transplanted Animals

In addition to their unique functional properties, DLs display migratory patterns that are distinct from those of other leukocytes. These migratory properties almost certainly play an important role in the initiation of immune responses (including allograft rejection).

TABLE 2. *Phenotype and Function of Dendritic Leukocytes*

Phenotype (monoclonal antibody)	Cardiac DL (<i>in situ</i>)	Langerhans cells (<i>in situ</i>)	Langerhans cells (cultured)†	Lymphoid DC (isolated)
Leukocyte common antigen (TIB 122)	+	+	+	+
MHC class II (B21-2, MKD6, 10-2.16)	+	+	+	+
Complement receptor-C3Bi (M1/70)	+	+	+	+
Fc receptor type II (2.4G2)	+	+	—	—
F4/80 antigen (F4/80)	—	+	—	—
IL-2 receptor light {p55} chain (7D4)	—	—	+	+
CD4	—	—	—	—
CD8	—	—	—	—
Immunoglobulin	—	—	—	—
Function				
Antigen processing†	?	+	—	—
Immunostimulation	+*	—	+	+

* After overnight culture, † originally described in reference 16.

† Reference 17.

Two pathways by which DLs move between tissues have been defined in normal rodents. For some time it has been known that DLs migrate out of tissues as 'veiled cells' in the afferent lymph.²⁵⁻²⁷ Apparently mature DCs also can be isolated from human peripheral blood¹⁴ and experimentally when mature DCs are injected intravenously into syngeneic or allogeneic mice or rats they migrate primarily to the spleen.^{28,29} Within the spleen the cells localize next to T cells in the white pulp.³⁰ Interestingly entry of DCs from the blood into the spleen is dependent on the presence of T cells, suggesting that T cells may recruit circulating DCs, conceivably by modifying receptors on the endothelium.

In light of the latter finding, we reasoned that in transplanted animals recipient DCs might be recruited to the graft by infiltrating T cells. There the DC could acquire graft antigens and sensitize T cells. However this proved not to be the case. When radiolabeled mature DCs of recipient strain were injected into the blood of animals bearing cardiac or skin grafts, we could not detect migration into either allografts or isografts of these tissues,¹¹ but they migrated from the blood to the spleen as in unmanipulated animals. In contrast the accumulation of resting and sensitized T cells was readily detectable in the same cardiac or skin allografts.

Migration of DLs from nonlymphoid peripheral tissues *via* the lymph and the blood into lymphoid tissues is apparently a mechanism whereby antigens are transported from the periphery into lymphoid tissues to allow the generation of immune responses. In the setting of transplantation, similar migration of donor DL might also be expected. The juxtaposition of donor DLs next to recipient T cells in the lymphoid tissues could provide a potent route of sensitization against graft antigens.

To address this possibility studies were undertaken to determine whether donor DLs could also migrate from vascularized organ allografts *via* the blood into the recipients' spleens after transplantation.¹² By taking advantage of monoclonal antibodies that recognized donor but not recipient DLs, we were able to show that there was rapid efflux of donor DLs from vascularized murine cardiac allografts that occurred during the first 4 to 5 days after transplantation (Fig. 1). A similar reduction in the number of DLs in rat cardiac allografts and isografts has also been noted by others.³¹

By examining the spleens of the recipients with the same monoclonal antibodies, we found dendritic-shaped cells that expressed high levels of donor MHC class II appearing in the recipients' spleens during the same time period that they were leaving the grafts (Fig. 1). Recently we found another description of donor MHC class II-positive cells migrating to the spleen after cardiac transplantation in the rat, but the origin of these cells was not defined clearly.³² Using double-labeling techniques we found the

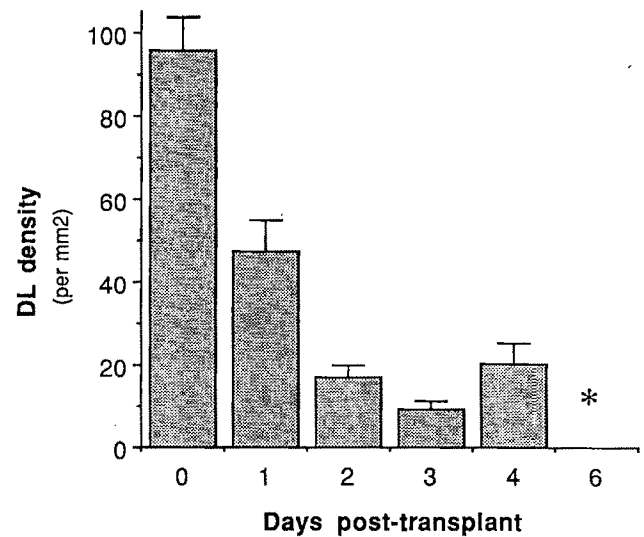


FIG. 1. Donor DLs migrate rapidly out of cardiac allografts. BALB/c (H-2^d) hearts were transplanted as fully vascularized, heterotopic (abdominal) grafts into C3H/He recipients, essentially as described,³² with additional precautions to minimize the transfer of donor blood within the grafts.¹² At the specified intervals the grafts were removed, sectioned, and stained with anti-donor Ia antibodies using immunoperoxidase techniques. There was a rapid and striking efflux of donor DLs from the grafts. At later times (*) Ia induced on other graft elements precluded quantitation of the donor DL.⁵³

donor DLs to be localized within the peripheral white pulp of the spleen. In addition to determining their microanatomic localization, 78% of the donor DLs were found to be in contact with recipient CD4⁺ T cells within the peripheral white pulp. Interestingly the donor DLs were found only rarely in contact with CD8⁺ T cells. The juxtaposition of donor DLs next to recipient CD4⁺ suggests that the spleen is potentially an important site of sensitization because activated CD4⁺ cells play a critical role in allograft rejection.³³

Phenotype and Function of Isolated Cardiac Dendritic Leukocytes

To better understand the nature of the DLs contained within transplanted tissues, we examined the phenotype of cardiac DLs in tissue sections using two-color immunofluorescence (Table 2). The cardiac DLs displayed a phenotype closely resembling that of the LCs of skin expressing MHC class II molecules, Fc receptors (type II), the leukocyte common antigen and low levels of the complement receptors (CR3bi), and no detectable IL-2 receptor (low-affinity chain). The only notable difference was the absence of the F4/80 antigen, which is expressed on epidermal LCs and many macrophages. In contrast lymphoid DCs express MHC class II molecules, the leukocyte common antigen, the IL-2 receptor, low levels of the complement receptor but do not express Fc receptors, or the F4/80 antigen.

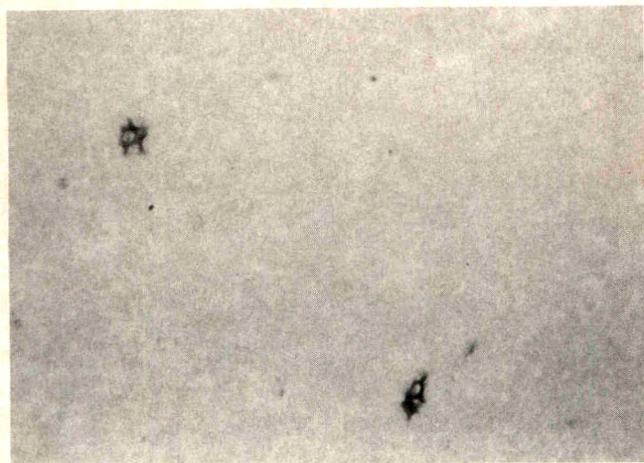


FIG. 2. Donor DLs migrate into the recipients' spleens. At the same time donor DLs were leaving the allografts, similar donor Ia^+ cells with dendritic morphology entered the recipients' spleens. The figure shows two Ia^d -positive cells within the spleen of a CBA/Ca ($H-2^k$) recipient of BALB/c cardiac allograft 2 days after grafting (250 $\times$).

One of the critical questions that remained was whether the cardiac DLs possessed (or could acquire) the ability to activate resting T cells. If so this would suggest that the migration pathway outlined above might be an important route of sensitization. To address this issue we examined the functional properties of DLs isolated from normal mouse hearts. The hearts were digested with collagenase, trypsin, DNase, and ethylene-dinitrilo tetraacetic acid (EDTA) to produce single-cell suspensions using a procedure originally described for the isolation of mesengial cells from mouse kidneys. These suspensions were cultured overnight and the DLs were isolated from the sus-

pension by density centrifugation on bovine serum albumin gradients,³⁴ followed by panning with anti-Ia antibodies.²² Cytocentrifuge preparations revealed that $\sim 85\%$ of the cells isolated in this manner were strongly Ia-positive leukocytes.

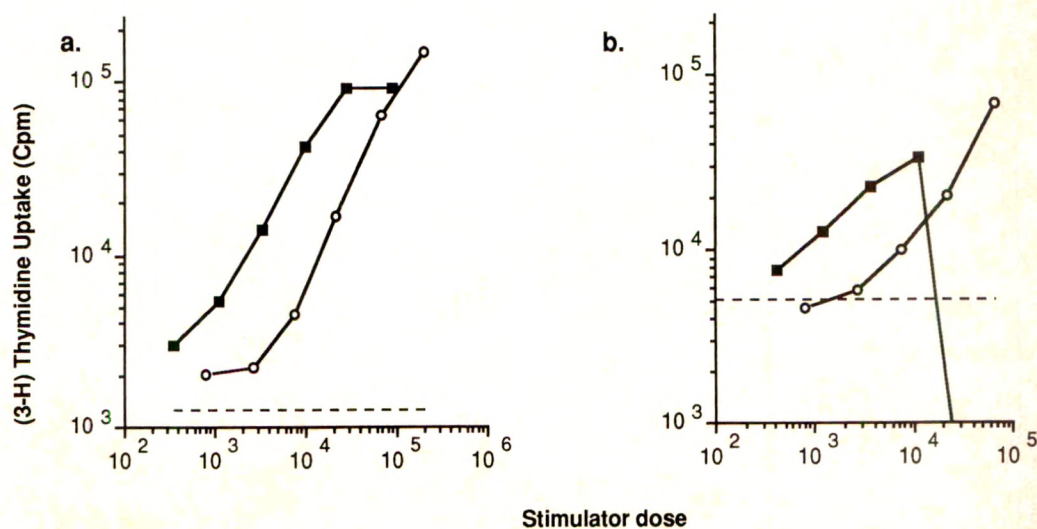
The isolated cardiac DLs were tested for their ability to stimulate syngeneic T cells, modified by sodium periodate (oxidative mitogenesis) (Fig. 3A) or untreated allogeneic T cells in a mixed leukocyte reaction (Fig. 3B). Oxidative mitogenesis is a rapid, well-characterized response that is exquisitely sensitive for detecting the presence of immunostimulatory cells (DCs).^{35,36} As shown in Figure 3, isolated cardiac DLs were potent stimulators of both types of responses and were 5 to 10 times more potent than splenocytes on a per-cell basis. At higher doses the cardiac populations appeared to produce toxic effects, particularly in the allogeneic T-cell responses, and this seems to be largely due to a contaminating adherent population that requires further study.

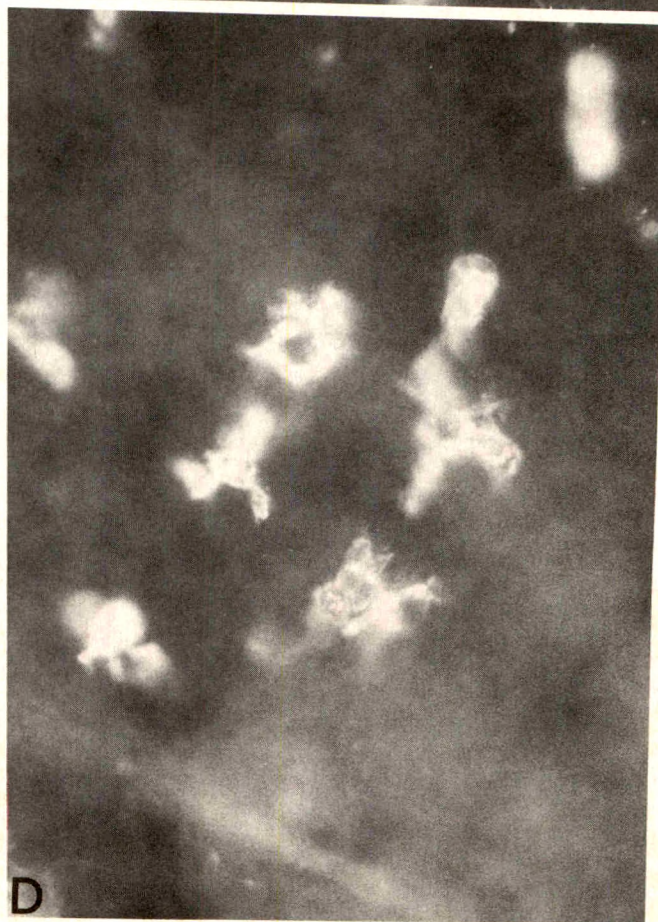
Most importantly the ability of isolated cardiac DLs to stimulate resting T cells indicates that the migration of donor DLs out of cardiac allografts into the spleen is likely to be an important pathway leading to activation of alloreactive recipient $CD4^+$ T cells.

Phenotype and Function of Migrating Langerhans Cells in Organ Culture

To study the regulation of DL migration and function in more detail, we have turned to a system that is more amenable to manipulation and have examined the LCs in skin grafts and in a skin-organ culture system (manuscript submitted for publication). We previously observed

FIGS. 3A and B. Cardiac DL are potent stimulators of primary T-cell responses; (a) oxidative mitogenesis and (b) allogeneic mixed leukocyte reactions. Cardiac DL were isolated from the hearts of normal C57BL/10 ($H-2^b$) mice using digestion steps with collagenase, DNase, and Trypsin and EDTA, followed by density gradient separation over bovine serum albumin,³⁴ and specific isolation of the Ia^+ cells with antibody panning techniques.²² Graded doses of irradiated (2000 rads ^{137}Cs) cardiac DL (filled squares) or splenocytes (open circles) (both C57BL/10) were added to a) syngeneic sodium periodate-treated T cells or (b) untreated allogeneic (C3H/He, $H-2^k$) resting T cells (2.5×10^5 /well) in a final volume of 0.2 mL in 96-well flat bottom microtest wells. The dashed line indicates the ^3H thymidine uptake of the responders (T cells) alone. Proliferation in the wells was measured by adding 1 μCi of ^3H -thymidine per well after 22 to 26 hours, for oxidative mitogenesis or after 96 hours for allo MLRs. The cells were harvested 16 to 18 hours later and counted on an LKB beta plate counter. Results are the means of triplicate cultures.





FIGS. 4a–d. Langerhans cells migrate from the epidermis of cultured skin. Langerhans cells (stained with anti-Ia) within epidermal sheets of cultured C57BL/10 ear skin. (a) Normal skin has an extensive network of LC; (b) after 4 hours in culture the LCs are larger and express higher levels of Ia; (c) after 24 hours the cells remain large but begin to decrease in numbers; and (d) by 3 days most LCs have migrated out of the epidermis and are found in the dermis or in the media (not shown). Mouse ear halves were cultured as described in Figure 5 legend. Epidermal sheets were prepared from the cultured ears with 0.5 mmol/L ammonium thiocyanate for 20 minutes at 37°C.⁵⁴ The epidermal sheets fixed in acetone for 20 minutes, rehydrated in PBS, and incubated with B21-2 (anti-Ia^{b,d}) for approximately 16 hours at 4°C. After washing in PBS containing 1% FCS, 0.01% NaN₃, they were incubated in FITC-conjugated mouse anti-rat IgG (Boehringer-Mannheim, FRG) at 1:100 for 90 minutes at 37°C, washed three additional times, and mounted. Epidermal and dermal sheets were evaluated under a Leitz Ortholux II UV microscope (Leitz, FRG).

that in skin grafts epidermal LCs increase in size, increase their expression of Ia, and then migrate from the skin *via* the dermal lymphatics. Virtually identical changes to these were observed in the skin–organ culture system (Fig. 4), and ultimately LCs migrated from the skin into the culture media. These changes occurred rapidly, the upregulation of MHC class II occurring within hours, and migration commencing within 24 hours. The stimulus for LC migration is apparently part of the ‘nonspecific’ response to injury because similar LC migration has been noted in isografts and allografts as well as in organ culture. The latter indicates that migration is stimulated by a locally produced mediator.

The migration of LCs in skin–organ culture was accompanied by phenotypic and functional maturation of the LCs into cells more closely resembling lymphoid DCs. Most importantly during their migration out of the skin, the LCs matured into extremely potent stimulators of oxidative mitogenesis and allogeneic mixed leukocyte re-

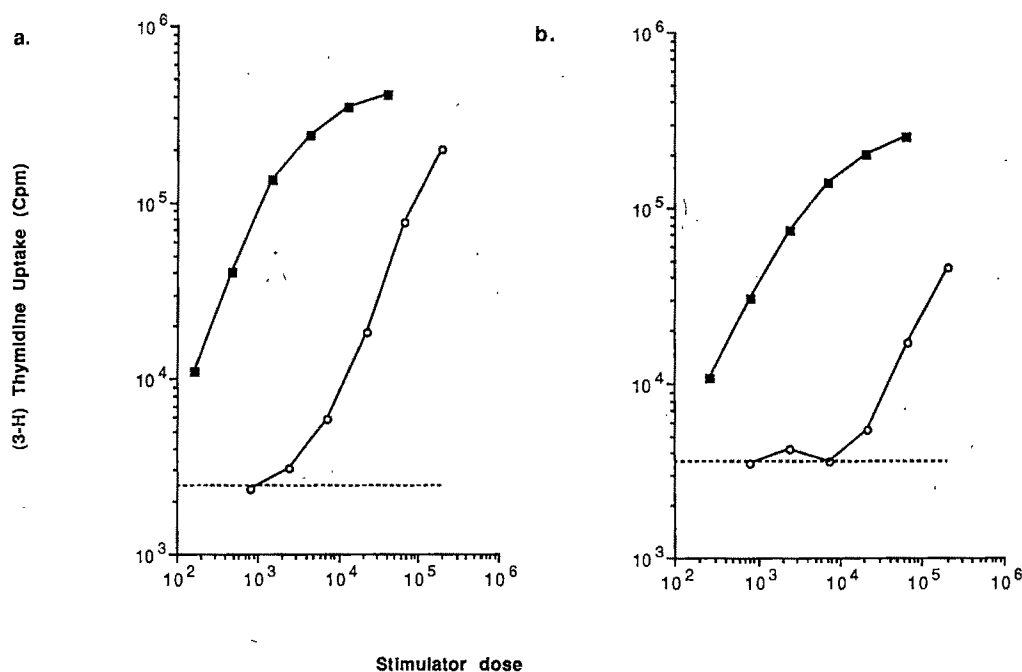
actions (Figs. 5a and b). The cytokines GM-CSF, IL-1, and TNF- α have been identified as factors that promote either maturation of DLs into potent stimulators or enhance viability in culture.^{22,37} We are trying to determine whether these cytokines and/or others also regulate the migration this potent group of immunostimulatory cells.

Discussion

It is now clear that DLs are contained within essentially all transplanted organs. These cells are very plentiful in heart, kidney, liver, and pancreatic islets and are not a ‘trace’ cell population, as they are commonly regarded. The DLs of nonlymphoid tissues appear to have a phenotype that is similar to that of the LCs of skin, with the interesting exception of the liver, in which DLs appear to express the phenotype of lymphoid DCs.^{38,39} Isolated cardiac DLs (and kidney DLs, unpublished data) are potent stimulators of resting allogeneic T cells and periodate modified syngeneic T cells.

FIGS. 5A and B. Langerhans cells mature into potent stimulators of primary T-cell responses during their migration out of skin; (a) oxidative mitogenesis and (b) allogeneic mixed leukocyte reactions. (a) Graded doses of irradiated (2000 rads ¹³⁷Cs) LCs (filled squares), or splenocytes (open circles) (both BALB/c) were added to (a) syngeneic sodium periodate-treated T cells or (b) A/J (H-2^a) LCs (filled squares) or A/J splenocytes (open circles) added to untreated allogeneic (BALB/c, H-2^d) resting T cells (2.5×10^5 /well) in a final volume of 0.2 mL in 96-well flat bottom microtest wells. The dashed line indicates the ³H thymidine uptake of the responders (T cells) alone.

To obtain LC populations, BALB/c mouse ear halves were cultured by floating individual ear halves on 2 to 2.5 mL of complete media RPMI 1640, 10% fetal calf serum, 2 mmol/L glutamine, 45 μ g/mL penicillin, 45 μ g/mL streptomycin, and 90 μ g/mL kanamycin in 24-well plates for 4 days. Migratory LCs were harvested from the culture wells, filtered through a 35- μ m nitex filter (Tekto Inc., New York, NY) to remove hair and debris from the cultured ears, pelleted, and counted in trypan blue before use. Cell populations obtained using this system were 60%–70% Ia⁺ LCs (manuscript submitted for publication). The assays were conducted as described in Figure 3 legend, except that the allogeneic mixed leukocyte proliferation was measured at 72 hours.



The transplantation procedure itself promotes rapid migration of donor DLs out of cardiac allografts and into the spleen. Older studies in large animal models demonstrated cells with the appearance of DLs ('cells with exuberant cytoplasmic veils') in the afferent lymph-draining renal allografts.⁴⁰ Injection of these cells provoked a 'vigorous cellular reaction' in the draining lymph node. Although these studies were performed before the description of DLs, the findings strongly suggest that DLs also can leave vascularized allografts *via* the lymphatics and presumably migrate into the draining lymph node.

The rapidity of the migration of DLs out of transplanted tissues and their juxtaposition next to recipient T cells suggests that this pathway may be involved in the early post-transplantation rejection episodes that remain a significant clinical problem. This idea is supported by the findings of an initial pilot study and more recently a prospective randomized clinical trial that demonstrated a significant reduction in the number of acute rejection episodes in renal allograft recipients whose grafts had been pretreated using a protocol to deplete 'passenger leukocytes'.^{41,42}

The effect of donor DLs may not necessarily be confined to the peritransplant period, however. In nonrejecting animal transplant models, a proportion of donor DLs remained within skin or cardiac allografts or skin xenografts for at least 6 months after transplantation.⁴³⁻⁴⁵ It is possible that donor DLs may persist within allografts in immunosuppressed patients as well, but this must be explored.

An obvious question raised by our findings of the migration of donor DLs into the host spleen is that of the role of splenectomy. Experimental studies on splenectomy in rats bearing renal and cardiac allografts have shown marked prolongation or indefinite graft survival in some strain combinations,⁴⁶ but only a slight prolongation or no effect in others.⁴⁷ Prospective randomized clinical trials have demonstrated an initial positive effect of pretransplant splenectomy on graft survival⁴⁸ and severity of rejection.⁴⁹ However at 6 years graft survival was no longer significantly better in splenectomized patients.⁵⁰ Thus while pre- or peritransplant splenectomy clearly has an effect on the rejection process, by itself it is not sufficient to prevent sensitization.

There are at least two possible explanations for the observations regarding the effect of splenectomy. First, it may be that donor DLs leave the graft *via* the lymph as well as *via* the blood (see above). Interruption of either pathway alone would be unlikely to have a major effect on the sensitization process. Second, it is possible that other mechanisms can lead to sensitization; in particular it is possible that recipient DLs can process and present donor antigens and initiate allograft rejection, and there is limited data in support of this idea.⁵¹ The animal data, however, suggest that while processing by host DLs may

occur, it is probably less efficient than direct sensitization by donor DLs.^{4,6,7,10}

Clinical application of the lessons learned from the animal studies on the role of passenger DLs has remained an elusive goal. We are encouraged by the data from the clinical trial demonstrating an effect of passenger leukocyte depletion. However the authors have acknowledged that there are technical problems with this depletion protocol and animal studies have suggested that near-complete elimination may be required for beneficial effects to be seen.⁶ If these protocols are to be applied on a large scale clinically, continued research into methods to improve the level and consistency of depletion will be required.

The evidence that DL function by maturing into potent immunostimulatory cells and migrating into lymphoid tissues suggests that there may be alternative strategies for interrupting sensitization. By studying the mediators that regulate the migration and maturation of DLs, it may become possible to devise protocols to deplete grafts of DL by inducing their migration or to prevent their maturation into potent immunostimulatory cells after transplantation.

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DISCUSSION

DR. NICHOLAS L. TILNEY (Boston, Massachusetts): I was delighted to have the opportunity to discuss this paper from this particular group, who have been working on these curious dendritic cells for several years now.

As we have heard, acute allograft rejection is mediated primarily by T lymphocytes. Once activated by graft antigen, many of these cells develop the capacity to elaborate lymphokines, active effector molecules.

In contrast, dendritic cells have no recognized effector function but appear to be specialized immunostimulatory cells that can activate resting T lymphocytes.

Theoretically, by removing such cells from the graft, as we have heard, an important trigger for rejection can be blocked, with resultant graft prolongation.

If dendritic cells are so critical, my first question is: Why is graft prolongation not more reproducible in various transplant models from which such cells in the grafts have been removed or destroyed?

Dendritic cells in normal or transplanted animals migrate from tissue to tissue, apparently via blood stream and lymph, a physiologic process that may amplify sensitization of the host against antigenic stimuli.

In this paper Dr. Larsen and his colleagues distinguish nicely between donor and recipient dendritic cells. An obvious criticism, however, of any dendritic cell work is that there is no specific marker for these cells, and they can only be identified by negative selection. That is, all other identifiable cell populations are removed, leaving behind only putative dendritic cells, which are then stained. The obvious question, of course, is: Are these really dendritic cells?

The investigators have also shown that dendritic cells migrate from graft to spleen, an observation at variance with the usual dogma that suggests that sensitization of host cells occurs within the graft itself and not within lymphoid tissues of the host.

If this migration pathway to spleen is so important, why are the results of recipient splenectomy so variable, extending graft survival in some models but not in others?

This slide shows isologous mouse spleen dendritic cells, the blue spots, which migrate to normal splenic white pulp. To emphasize how effete this cell population is, it takes about ten mouse spleens at about 100 million cells apiece to produce a million of these blue dendritic cells.

In this paper, the authors have shown differences between cells such as these dendritic leukocytes and donor cells migrating from heart graft to spleen. Do these two dendritic cell populations have differential migration patterns? Specifically, do they go to different anatomic compartments in the white pulp of the spleen?

And finally the question of phenotype arises. As we have heard, Langerhans cells, maturing in culture, change their phenotype. Do you have any evidence that maturing cardiac dendritic cells do the same?

DR. MARK A. HARDY (New York, New York): I have shared with the Oxford group an interest in dendritic cells and particularly their migration and homing, not only because this is important for the understanding of antigen recognition and of mechanisms of rejection but also for the practical reason that this may offer approach to prolonging allografts without toxic immunosuppression of the host, perhaps even by manipulation of the donor organ itself.

I do, however, have some questions that are in many ways similar to Dr. Tilney's comments and questions.

We also have shown in the past that the donor organ, the cardiac allograft, quickly depletes itself of donor-type dendritic cells that go to the spleen. We do not quite understand, however, why these dendritic cells do not also go to lymph nodes, and they in fact do go there sometimes, particularly when a splenectomy is done. I wonder if the authors could comment on whether there is any special attraction about the spleen and whether there are chemotactic factors that attract these dendritic cells or antigen-presenting cells, which may be a better name for these cells, to the spleen, rather than to the lymph nodes.

The other question is, why doesn't the recipient antigen presenting cell go to the graft where there are already T cells with the appropriate receptors? Why don't the recipient dendritic cells go to the donor graft and offer a different pathway of transmission of information, an alternate pathway, if you will?

And finally, I would like to have Dr. Larsen comment about peripheral sensitizations, even though he emphasizes the centralization concept, as we have in our work over the past many years. How does he explain the findings of others in terms of peripheral sensitization using the sponge matrix models and other models, where most of the sensitization may occur, in fact, in the donor graft?

Is there a relationship between the central sensitization and the peripheral sensitization, particularly in regard to the antigen presenting cells, and is that correlation important regarding timing?

DR. ROBERT J. CORRY (Iowa City, Iowa): During the mid-1970s we were involved in protocols of donor pretreatment with cytoxan and steroids to eliminate passenger leukocytes with very little improvement in graft survival, if any, and I am wondering if we should reconsider those efforts.

You and others have shown that suppressor cells are produced in the spleen. Does the antigen-presenting cell have any role in creation of the suppressor cells?

The other new, novel Japanese drug, 15-deoxyspergualin, seems to affect the antigen-presenting cell, and I am wondering if you have any plans to use that drug experimentally.

DR. JOSHUA MILLER (Miami, Florida): The paradox in transplantation has always been with the antigen-presenting cell being of donor origin, whereas in all other immune responses the antigen-presenting cell is of recipient origin, where the co-recognition of the MHC class 2 by the helper T cell is always in what is called a restrictive pattern. That is, the recipient has to recognize recipient (autologous) MHC.

In my mind this has always been a paradox, and I would like to know if in your paper you have dealt with this paradox. Have you looked at—this is to amplify Mark Hardy's point—the recipient antigen-presenting cells? What happens to them in the spleen in relationship to the donor APCs?

DR. CHRISTIAN P. LARSEN (Closing discussion): First I would like to address Dr. Tilney's question as to why we consider the Ia⁺ leukocytes of heart to be dendritic leukocytes (DL). Work on DL has been hampered by the lack of DL-specific monoclonal antibodies, which stain DL of nonlymphoid tissues. However, we have presented evidence that the DL of heart are phenotypically extremely similar to the Langerhans cell of skin (the DL of the epidermis). In addition, we have shown with two-color immunofluorescence that the cardiac DL do not express B-cell, T-cell, and some conventional macrophage markers (F4/80).

In addition, as Dr. Tilney mentioned, classic splenic dendritic cells do not display effector functions, which distinguishes them from macrophages. Similarly Hart and Fabre have shown that the DL of heart are nonphagocytic. In the studies reported here, we have isolated the DL from heart and found that, like classic dendritic cells, these cells possess immunostimulatory activity, that is, the ability to initiate a primary T-cell response. Therefore the DL of heart are phenotypically and functionally very similar to dendritic cells from lymphoid tissues.

Next I would like to address why depletion of donor DL from grafts prior to transplantation does not consistently lead to long-term graft survival. In many animal models if one can remove the donor DL prior to transplantation, prolonged graft survival can be obtained. However, this is not uniformly the case. One reason for these inconsistencies was suggested by Derek Hart, who found that in order to achieve an effect, 95% of the donor DL had to be depleted. So, one answer is that in some studies there may not have been adequate DL depletion. However, this is clearly not the whole answer, because there have been very carefully performed studies where near complete DL depletion has been achieved, and yet the grafts are still rejected.

This leads us to the question of whether or not host DL are involved in rejection. There is limited *in vitro* and *in vivo* evidence that in some cases that host DL can process and present graft antigens to host T cells and initiate an anti-donor response. However it appears from the depletion studies that in most cases that presentation by host cells is a weaker route of sensitization, hence our interest in donor DL.

The question regarding the role of splenectomy is particularly pertinent in light of the migration of donor DL into the spleen. Splenectomy has been investigated both experimentally and clinically in prospective ran-

domized trials. In many rat transplantation models splenectomy results in prolonged graft survival, and in man renal allograft survival was improved at 2 years in splenectomized patients. In both cases, however, it is clear that splenectomy alone does not prevent sensitization.

There are at least two possible explanations for this observation. DL can leave tissues via the lymph, as well as via the blood. Therefore, it seems likely that the donor DL migrate not only to the spleen, but also to the lymph nodes, as lymphatic connections are re-established. There, they might sensitize recipient T cells. Alternatively, host DL in lymph nodes may be involved in sensitization.

Dr. Tilney has noted that there are subtle differences in the localization of DL within the spleen in the present study and a previous study from our group (*J Exp Med* 1988; 167:646-651). In the earlier study, syngeneic splenic dendritic cells localized primarily in the central white pulp, whereas in this study the allogeneic cardiac DL localized in the peripheral white pulp. At present we do not have an explanation for this interesting difference. One possibility is that donor DL enter the spleen at the marginal zone. During their migration toward the central white pulp they may encounter alloreactive T cells that arrest further migration.

Dr. Hardy noted that dendritic cells fail to migrate into lymph nodes from the blood. This was shown in the studies by Drs. Austyn and Kupiec-Weglinski. From the blood, dendritic cells migrate exclusively into the spleen, the entry into spleen being T-cell dependent. When DL are injected into nude, T-cell-deficient mice, they fail to home to the spleen,

but if the animals are reconstituted with T cells, the DL home to the spleen as in normal animals. So it appears that T cells within tissues might be able to alter the endothelium to promote recruitment of dendritic cells.

This point also relates to question of whether recipient DL migrate into allografts. We have investigated this question using ¹¹¹Indium-labeled host-strain dendritic cells. We found that mature DC did not migrate into cardiac allografts in the early postoperative period after transplantation. In this setting, even though T cells were present in the grafts, host DC were not recruited.

In the long term, if an allograft is accepted, there is evidence that recipient DC do eventually repopulate grafts. Based on our data, we would predict that during the generation of immune responses, such as allograft rejection, that they too would migrate centrally.

Finally Dr. Hardy has noted that, in contrast to our data, studies using sponge-matrix allografts have suggested that site of sensitization is primarily peripheral, in the graft. There may be important difference between sponge matrix grafts, which are often prepared with donor splenocytes, and vascularized organ allografts that contain nonlymphoid DL, akin to Langerhans cells. As we discuss in the manuscript, DL in the periphery cannot initiate immune responses unless they are stimulated by the cytokine GMSCF, whereas splenic DC are mature immunostimulatory cells. Therefore sponge-matrix allografts may contain a different population of DL than those normally present in allografts.

Partial Ileal Bypass for Hypercholesterolemia

20- to 26-year Follow-up of the First 57 Consecutive Cases

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JOHN P. MATTS, PH.D., and RICHARD L. VARCO, M.D., PH.D.

Between 1963 and 1968, 57 patients underwent partial ileal bypass (PIB) at the University of Minnesota for primary hypercholesterolemia. Preoperative total plasma cholesterol (TC) was 363.3 ± 136.8 mg/dL (mean $\pm$ SD) in these patients. Baseline and follow-up TC results demonstrated highly significant ($p \leq 0.001$) TC reduction, 34% ($n = 48$), 28% ($n = 49$), 35% ($n = 26$), 35% ($n = 11$), and 30% ($n = 25$) at 1, 2 to 5, 6 to 10, 11 to 15, and more than 20 years, respectively, after PIB. In 21 patients with baseline, 1-year, and more than 20-year results, TC decreased 33% by 1 year and remained 29% less than baseline more than 20 years after surgery ($p = \text{NS versus 1 year}$). Plasma triglyceride results were available in fewer patients, and no statistically significant changes developed after PIB. Two patients (3.5%) underwent PIB reversal, one for intractable diarrhea and one for recurrent nephrolithiasis. In the 25 nonreversed, long-term survivors, no statistically significant weight change was noted. Twenty-four per cent had 0 to 2, 52% had 3 to 5, and 24% had more than 5 bowel movements per day. Subsequent cholecystectomy was required in eight patients, and nephrolithiasis developed in 10 (40%). During 20 to 26 years, most survivors developed clinically apparent atherosclerosis: angina (60%), myocardial infarction (16%), or coronary artery bypass (28%). Coronary heart disease was the predominant cause of death among nonsurvivors (80%). Overall survival rates were 95%, 88%, 75%, 59%, 53%, and 41% at 1, 5, 10, 15, 20, and 25 years, respectively, after PIB. Partial ileal bypass leads to highly significant TC reduction, which is sustained, essentially unchanged, more than 20 years after operation. In comparison to available epidemiologic and clinical trial data, these results support the hypothesis that TC reduction has a beneficial effect in patients with hypercholesterolemia.

SINCE THE INITIAL induction of atherosclerosis by cholesterol feeding in rabbits by Anitschkow in 1913, the causal relationship between cholesterol and experimental atherosclerosis clearly has been established.¹ Epidemiologic analyses, including the Seven Countries Study,² the Framingham Study,³ and the Pooling Project,⁴ have confirmed this relationship in humans. The screening results of the Multiple Risk Factor Inter-

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vention Trial precisely related the total serum cholesterol level and the subsequent, 6-year coronary heart disease (CHD) mortality rate in 361,662 asymptomatic men.⁵ Those with total serum cholesterol levels between 203 and 221 mg/dL had 1.7 times the 6-year CHD mortality risk, those with total serum cholesterol levels between 222 and 245 mg/dL had 2.2 times the 6-year CHD mortality risk, and those with total serum cholesterol levels greater than 264 mg/dL had more than four times the 6-year CHD mortality risk compared to men with total serum cholesterol levels less than 181 mg/dL. Despite modifications of CHD risk factors and improvements in medical care that have led to progressive decreases in annual CHD mortality rates, CHD remains the leading cause of death in the United States and in the western world, surpassing the number of deaths due to all forms of cancer combined.⁶ Among the major, modifiable CHD risk factors, hypercholesterolemia, hypertension, smoking, and diabetes, the critical importance of hypercholesterolemia is evident. It is estimated that one fourth of the adult United States population, nearly 40 million people, have total plasma cholesterol levels greater than 240 mg/dL, placing them at significantly increased risk for death due to CHD.⁷ Detection and treatment of hypercholesterolemia has become the focal point of recent public health initiatives to reduce the CHD mortality rate in this country and abroad.^{8,9}

In May 1963, after completion of rabbit and swine experiments demonstrating that cholesterol and bile acid absorption from the intestinal tract, as well as plasma cholesterol levels, were significantly reduced, without concomitant weight loss, after diversion of substantial lengths of the distal small bowel,^{10,11} we performed the initial partial ileal bypass (PIB) specifically for cholesterol reduction in humans.¹² Subsequently more than 600 PIB procedures have been performed worldwide.¹³⁻¹⁸

In 1989 we completed this review of the initial 57 patients undergoing PIB between 1963 and 1968 to examine the long-term effects of this operation on plasma lipid levels, nonatherosclerotic morbidity and mortality, and

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atherosclerotic morbidity and mortality. Although dietary and pharmacologic approaches have assumed the predominant role in the current management of hypercholesterolemia,⁸ there is no report of the effects of any intervention to reduce cholesterol levels with follow-up extending beyond 20 years. Despite lack of a concurrent, randomized control group, the present analysis can provide insight into the potentially beneficial effects of long-term lipid intervention on the course of nonatherosclerotic and atherosclerotic disease in patients with hypercholesterolemia.

Methods

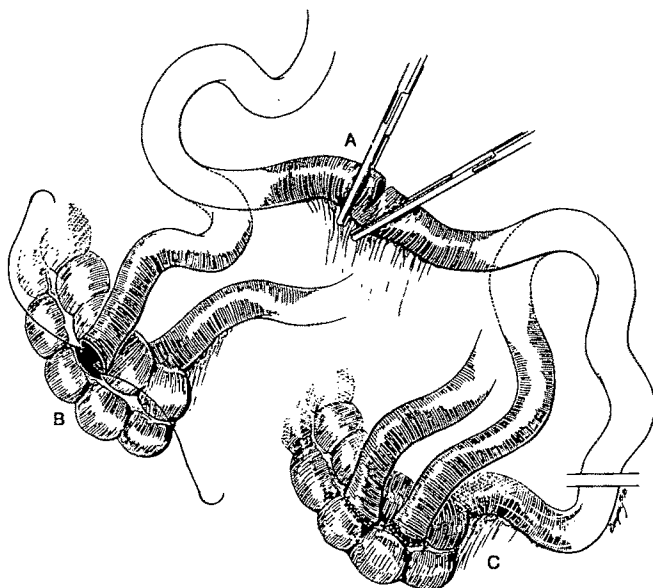
Operative Procedure

Between May 1963 and December 1968, 57 patients underwent PIB for the treatment of primary hypercholesterolemia. The operation was conducted in a similar manner in all patients (Fig. 1). Before operation intestinal preparation was begun, at least overnight, with a clear liquid diet, nonabsorbable oral antibiotics, and cathartics. Cleansing enemas were not used. The abdomen was entered through a transverse right lower quadrant incision approximately 2 cm below the umbilicus, unless a concomitant procedure such as a cholecystectomy was planned, in which case an upper transverse or a midline abdominal incision was used. After routine abdominal exploration, the total small bowel length was measured

along the mesenteric border using a calibrated umbilical tape, allowing 25 cm for the duodenal length. The small bowel was transected 200 cm proximal to the ileocecal valve or at a point one third the total small bowel length proximal to the ileocecal valve if the total small bowel length was more than 600 cm. Although stapling instruments can be used, we have preferred clamps with hand-sewn, two-layer intestinal anastomoses and closures. The distal ileal segment was closed with a running inner absorbable layer and an interrupted outer nonabsorbable layer placed in Lembert fashion. The proximal small bowel segment was anastomosed, end-to-side, into the anterior taenia of the cecum approximately 6 cm distal to the inverted appendiceal stump using a two-layer technique. If present, the appendix was removed routinely. The cecum was chosen as the site of anastomosis to maximize the colonic, water-absorptive surface area. The anastomosis was made distal to the ileocecal valve to minimize ileal retention of chyme with absorption of cholesterol and bile acids. The previously closed end of the bypassed distal segment was tacked to the anterior taenia of the cecum between the anastomosis and the appendiceal stump to prevent intussusception of this segment. The small divisional and the large rotational mesenteric defects were closed to prevent internal herniation. The abdomen was copiously irrigated with antibiotic-containing normal saline solution and aspirated dry. After changing gowns and gloves, and using separate instruments, fascial closure was accomplished with interrupted, nonabsorbable sutures. The skin was reapproximated with interrupted, nonabsorbable sutures or with metal clips. Drains were not used routinely.

Follow-up Analysis

In 1989 the medical records of all 57 patients were reviewed, and the vital status of each patient was ascertained from autopsy reports or death summaries in the medical record, or by telephone contact with the patient or with his or her survivors. Baseline and follow-up lipid values were abstracted directly from laboratory reports in the medical record. Many patients were referred by community physicians and did not receive their routine medical care at the University of Minnesota. Consequently their lipid results are sporadic. At baseline and throughout the follow-up period, the lipid profile was obtained after an overnight fast and included routine determination of the total plasma cholesterol (TC) level and occasional determination of the plasma triglyceride (TG) level by the clinical laboratory of the University of Minnesota Hospital using standard clinical methodology. In addition to these lipid results, all surviving patients contributed a 1989 plasma sample for analysis of TC, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cho-



FIGS. 1A–C. Partial ileal bypass. (A) Division of the ileum 200 cm proximal to the ileocecal valve or one third of the total small bowel length proximal to the ileocecal valve if the total small intestinal length is greater than 600 cm. (B) End-to-side anastomosis of the proximal segment into the anterior taenia of the cecum, 6 cm distal to the appendiceal stump. (C) Tacking of the closed distal segment to the anterior taenia of the cecum midway between the anastomosis and the appendiceal stump.

lesterol, very low-density lipoprotein (VLDL) cholesterol, TG, apolipoprotein A-I, and apolipoprotein B-100. After at least a 14-hour fast, plasma samples were obtained at the University of Minnesota or in community physicians' offices and shipped to Minneapolis overnight in refrigerated containers. The 1989 lipid analyses were performed in the Central Lipid Laboratory of the Program on the Surgical Control of the Hyperlipidemias (POSCH) at the University of Minnesota using previously described techniques.¹⁹

In addition to plasma lipid analysis, a standardized questionnaire was administered in 1989 during a personal interview or by telephone to all patients who had not undergone PIB reversal. Body weight, current medications, and the nature of postoperative hospitalizations were recorded. Cardiovascular, peripheral vascular, and cerebrovascular morbidities were noted. Follow-up nonatherosclerotic data, including the occurrence of gastrointestinal, renal, and musculoskeletal events, and the development of any malignancy, were collected. Postoperative complications, including development of an incisional hernia or occurrence of an intestinal obstruction requiring operation, were recorded.

Statistical Methods

Continuous data are presented as the mean $\pm$ one standard deviation (SD). Group means were compared using one-way analysis of variance and paired or unpaired Student's *t* tests when appropriate. Total plasma cholesterol and TG percentage changes were calculated for each patient and averaged to provide an overall group value. During intervals in which several TC or TG results were available, the determination closest to the end of the interval was chosen. Survival analysis was performed using actuarial methods with the date of operation as the starting point and with reversed patients censored at the time of PIB reversal. A two-sided *p* value of less than 0.05 was considered statistically significant.

Results

Thirty-eight male (66.7%) and 19 female (33.3%) patients, with a mean age of 42.2 ± 10.4 years (range, 12 to 60 years), underwent PIB between 1963 and 1968. Excluding two patients undergoing PIB reversal 5 and 6 years after operation, the mean age at operation of patients surviving more than 20 years (40.0 ± 11.7 years, *n* = 25) was slightly less than in patients surviving less than 20 years (44.3 ± 9.2 years, *n* = 30); however this difference was not statistically significant (*p* = 0.13).

The TC results are summarized in long-term survivors in Table 1A, and in nonsurviving and reversed patients in Table 1B. Preoperative TC levels were available in all 57 patients, and the mean value (363.3 ± 136.8 mg/dL)

was significantly elevated (range, 200 to 1012 mg/dL). A follow-up TC level was available within the first postoperative year in 48 patients. Compared to the mean preoperative value in these patients, TC was significantly reduced (354.8 ± 139.7 mg/dL *versus* 231.1 ± 119.9 mg/dL, *p* = 0.0001), a $34.2\% \pm 17.7\%$ reduction (*p* = 0.0001). A follow-up TC level was obtained between 2 and 5 years after surgery in 49 patients. This value was markedly reduced from the preoperative level (360.0 ± 133.4 mg/dL *versus* 257.7 ± 130.2 mg/dL, *p* = 0.0001), a decrease of $27.7\% \pm 21.7\%$ (*p* = 0.0001). A 6- to 10-year follow-up TC level was available in 26 patients and was considerably lower than their preoperative values (324.9 ± 82.8 mg/dL *versus* 208.6 ± 73.4 mg/dL, *p* = 0.001), a reduction of $35.0\% \pm 16.6\%$ (*p* = 0.0001). Between 11 and 15 years after operation, a TC level was determined in 11 patients and was significantly reduced compared to the preoperative value (355.5 ± 102.6 mg/dL *versus* 231.9 ± 118.1 mg/dL, *p* = 0.004), a decrease of $34.5\% \pm 24.9\%$ (*p* = 0.001). A follow-up TC level was obtained in only five patients between 16 and 20 years after surgery, precluding meaningful statistical analysis.

Twenty-seven of the fifty-seven patients survived longer than 20 years. Excluding the two patients undergoing PIB reversal, the mean follow-up TC level obtained more than 20 years after operation was significantly reduced compared to the preoperative value (326.8 ± 88.1 mg/dL *versus* 219.0 ± 64.0 mg/dL, *p* = 0.0001), a $30.3\% \pm 19.6\%$

TABLE 1A. Total Plasma Cholesterol Results (mg/dL) in Long-term Survivors After Partial Ileal Bypass

Case	Baseline	Follow-up Interval (years)					
		1	2-5	6-10	11-15	16-20	>20
11	270	194	250	235			287
13	306	192	240	201			251
15	406		238	257			247
19	316		182	222			184
21	300	148	259				126
22	240		176	172	103		188
24	268	182	213			182	175
25	486	153	500				412
26	394	298	228				266
29	466	255	250	166	111		135
30	328	174	157				178
34	462	263					215
35	450	276	264				296
41	350	196					174
45	254	142		155	165		146
46	462		340				221
47	268	157	135	144	183	205	164
48	215	250					175
49	301	302	250				263
50	268	164	279				213
51	201	161	174	170			179
54	254	202	252	174	228		192
55	359	286	228	249	281	244	272
56	203	145	192				222
57	342	215	238				294

TABLE 1B. Total Plasma Cholesterol Results (mg/dL) in Nonsurvivors and Reversed Patients After Partial Ileal Bypass

Case	Baseline	Follow-up Interval (years)				
		1	2-5	6-10	11-15	16-18
1	558		297	332	315	
2	452	486	745	394	510	
3	378	313	268	416	292	274
4	402	195	186			
5	235	134	155	120		
6	333	192	189	207	127	170
7	404	250	260	172		
8	410					
9	364		145	137		
10	354	145	158	205		
12	298	123				
14	348	258	225	214	236	
16*	326		182			
17	270	174	172	169		
18	740	239				
20	314	158	140	140		
23	255	165	185	162		
27	432	288	290			
28	1012	878	815			
31	287	211	251	175		
32	468	290	405			
33	284	177	206	226		
36	368	170	184			
37	388	268	241			
38	353	378	327			
39*	200	155	207			
40	600		406			
42	540	360	292			
43	300	186	236			
44	340	188				
52	272	185	191	210		
53	254	170	222			

* Partial ileal bypass reversed.

decrease ($p = 0.0001$). In 21 of the 25 surviving, nonreversed patients, TC levels were available before operation, during the first postoperative year, and more than 20 years after surgery (Fig. 2). In these patients, the mean TC level decreased from 321.2 ± 87.6 mg/dL to 207.4 ± 54.2 mg/

dL ($p = 0.0001$) within the first postoperative year, a decrease of $33.0\% \pm 18.1\%$ ($p = 0.0001$). More than 20 years after surgery, the mean TC level was 220.7 ± 69.1 mg/dL, a decrease of $28.8\% \pm 20.4\%$ versus the preoperative value ($p = 0.0001$). The TC level more than 20 years after operation remained significantly lower than the preoperative level ($p = 0.0001$), but was not significantly changed from the TC level within the first postoperative year considered as an absolute value ($p = 0.43$) or as a percentage change ($11.1\% \pm 44.0\%$, $p = 0.26$).

To determine whether the TC change during the first year after PIB differentiates long-term survivors from nonsurvivors, the percentage change from the preoperative to the 1-year value was determined in long-term survivors ($-33.0\% \pm 18.1\%$, $n = 21$) and in the nonsurvivors ($-35.5\% \pm 17.7\%$, $n = 26$). These percentage reductions within the first postoperative year were not significantly different ($p = 0.63$).

The early and long-term TC results after PIB in male and female patients were examined (Table 2). During the first postoperative year, TC decreased significantly more in men than in women ($38.2\% \pm 17.1\%$ versus $27.5\% \pm 16.9\%$, $p = 0.04$). However, after the 20th postoperative year, the percentage reductions were similar in both sexes ($30.5\% \pm 21.0\%$ versus $31.6\% \pm 13.8\%$, $p = 0.90$). In the 21 nonreversed patients with TC levels before operation, within the first year, and more than 20 years after operation, no significant differences in the percentage reductions between the preoperative and 1-year TC level ($p = 0.79$), between the preoperative and the more-than-20-year TC level ($p = 0.70$), or between the 1-year and 20-year TC level ($p = 0.43$) were observed between male and female patients.

To determine whether the preoperative TC level influences the magnitude of TC change achieved by PIB, the TC results within the first postoperative year and more than 20 years after operation were examined in terciles

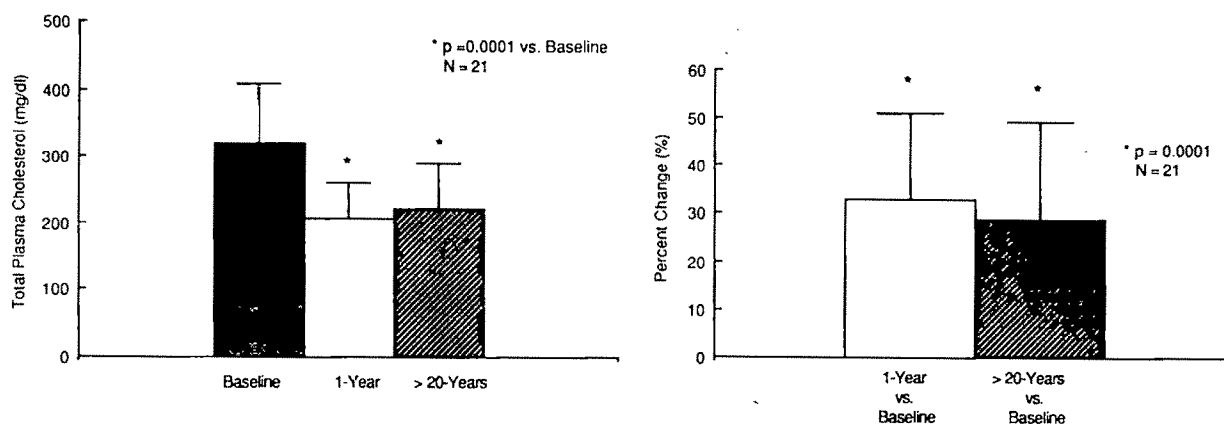
FIG. 2. Total plasma cholesterol results (mean $\pm$ SD) and percentage changes from baseline (mean $\pm$ SD) in 21 patients with baseline, 1-year, and >20-year results after partial ileal bypass.

TABLE 2. Total Plasma Cholesterol Results (mg/dL) After Partial Ileal Bypass by Sex

Patients with preoperative and 1-year results		
	Male (n = 30)	Female (n = 18)
Preoperative	348.4 ± 166.5	365.2 ± 80.5
1-year	210.8 ± 133.7	264.8 ± 85.3
% change	-38.2 ± 17.1*	-27.5 ± 16.9
Patients with preoperative and >20-year results		
	Male (n = 17)	Female (n = 8)
Preoperative	322.5 ± 98.8	335.9 ± 64.6
>20-year	214.6 ± 68.4	228.4 ± 56.6
% change	-30.5 ± 21.0	-31.6 ± 13.8
Patients with preoperative, 1-year, and >20-year results		
	Male (n = 13)	Female (n = 8)
Preoperative	312.2 ± 100.6	335.9 ± 64.6
1-year	195.0 ± 50.9	227.5 ± 56.7
% change vs. preoperative	-33.9 ± 20.0	-31.6 ± 15.9
>20-year	216.0 ± 77.5	228.4 ± 56.6
% change vs. preoperative	-28.0 ± 22.8	-31.6 ± 13.8
% change vs. 1-year	17.4 ± 54.4	1.4 ± 16.3

* p = 0.04.

based on the preoperative TC levels (Table 3). Although a tendency toward greater TC reduction in patients with the highest preoperative TC levels was evident within the first year and after the 20th postoperative year, no statistically significant differences were observed.

The impact of age at the time of surgery on the early and long-term TC results after PIB was examined in quar-

tiles based on age at operation (Table 4). Within the first postoperative year, PIB led to a smaller TC reduction in younger patients (age less than 30 years). More than 20 years after surgery, this trend toward reduced TC lowering in younger patients continued; however none of these differences between age quartiles achieved statistical significance.

Plasma triglyceride levels were obtained less frequently than TC levels in these patients (Tables 5A and B). A TG level was available at the time of PIB and within 1 year of operation in 22 patients. The mean TG level decreased (378.1 ± 434.1 mg/dL versus 308.7 ± 370.3 mg/dL, $p = 0.07$); however the overall percentage change ($1.8\% \pm 44.7\%$, $p = 0.85$) was not statistically significant. A TG level at operation and between 2 and 5 years after surgery was obtained in 23 patients. Mean TG decreased slightly (370.5 ± 426.0 mg/dL versus 298.0 ± 314.6 mg/dL, $p = 0.12$); however the $5.4\% \pm 50.0\%$ change from baseline was not statistically significant ($p = 0.61$). A baseline and 6- to 10-year TG level was determined in 11 patients. Mean TG was somewhat lower (440.3 ± 441.3 mg/dL versus 238.3 ± 110.6 mg/dL, $p = 0.10$), and the mean percentage reduction from baseline ($23.2\% \pm 38.8\%$, $p = 0.08$) approached statistical significance. Follow-up TG levels were available between 11 and 15 years and between 16 and 20 years after surgery in only five and three patients, respectively. This precluded meaningful statistical assessment.

A TG level at operation and 20 years or more after PIB was determined in 20 of the 25 surviving, nonreversed patients. Mean TG was somewhat lower (351.3 ± 444.9 mg/dL versus 229.3 ± 169.9 mg/dL, $p = 0.22$); however

TABLE 3. Total Plasma Cholesterol Results (mg/dL) After Partial Ileal Bypass by Preoperative Total Plasma Cholesterol Level

Patients with preoperative and 1-year results			
	≤300 (n = 20)	301-400 (n = 16)	>400 (n = 12)
Preoperative	257.8 ± 32.0	347.3 ± 27.1	562.2 ± 177.1
1-year	171.3 ± 29.3	233.3 ± 67.8	327.8 ± 192.1
% change	-32.5 ± 15.1	-32.9 ± 18.7	-38.6 ± 20.9
Patients with preoperative and > 20-year results			
	≤300 (n = 12)	301-400 (n = 8)	>400 (n = 5)
Preoperative	262.3 ± 54.3	337.0 ± 31.0	465.2 ± 13.1
>20-year	192.8 ± 44.1	235.3 ± 48.4	255.8 ± 104.3
% change	-24.4 ± 19.8	-29.9 ± 14.8	-45.2 ± 21.1
Patients with preoperative, 1-year, and > 20-year results			
	≤300 (n = 10)	301-400 (n = 7)	>400 (n = 4)
Preoperative	250.1 ± 32.9	340.0 ± 32.2	466.0 ± 15.0
1-year	174.5 ± 33.5	237.6 ± 55.5	236.8 ± 56.5
% change vs. preoperative	-28.8 ± 18.7	-30.0 ± 16.5	-48.9 ± 13.4
>20-year	187.9 ± 45.0	242.6 ± 47.3	264.5 ± 118.3
% change vs. preoperative	-23.3 ± 21.3	-28.2 ± 15.2	-43.5 ± 24.1
% change vs. 1-year	9.6 ± 26.7	4.3 ± 20.8	27.8 ± 96.9

TABLE 4. Total Plasma Cholesterol Results (mg/dL) After Partial Ileal Bypass by Preoperative Age

Patients with preoperative and 1-year results

	<30 (n = 7)	30-39 (n = 9)	40-49 (n = 12)	≥50 (n = 11)
Preoperative	447.3 ± 264.3	356.1 ± 165.0	337.6 ± 88.1	327.3 ± 71.1
1-year	367.9 ± 248.1	205.0 ± 46.0	209.3 ± 64.6	206.9 ± 72.1
% change	-19.2 ± 18.8	-37.2 ± 15.3	-37.3 ± 12.1	-35.2 ± 24.2

Patients with preoperative and > 20-year results

	<30 (n = 5)	30-39 (n = 4)	40-49 (n = 10)	≥50 (n = 6)
Preoperative	333.4 ± 94.0	320.0 ± 89.4	327.1 ± 84.9	352.2 ± 111.2
> 20-year	253.2 ± 33.7	256.5 ± 47.2	217.4 ± 77.5	168.2 ± 35.0
% change	-19.0 ± 22.8	-17.6 ± 17.3	-33.3 ± 13.4	-43.3 ± 20.9

Patients with preoperative, 1 year, and > 20-year results

	>30 (n = 5)	30-39 (n = 4)	40-49 (n = 8)	≥50 (n = 4)
Preoperative	333.4 ± 94.0	320.0 ± 89.4	318.6 ± 91.0	312.3 ± 108.3
1-year	242.2 ± 63.5	216.0 ± 40.2	183.8 ± 49.1	202.5 ± 57.9
% change vs. preoperative	-25.8 ± 16.9	-31.1 ± 8.5	-39.8 ± 15.2	-30.3 ± 31.3
> 20-year	253.2 ± 33.7	256.5 ± 47.2	217.9 ± 86.2	150.0 ± 23.2
% change vs. preoperative	-19.0 ± 22.8	17.6 ± 17.3	-31.6 ± 14.6	-46.6 ± 22.9
% change vs. 1-year	10.8 ± 32.1	20.2 ± 23.7	23.1 ± 60.5	-21.9 ± 21.9

the overall percentage change from the preoperative value was not statistically significant ($23.9\% \pm 111.1\%$, $p = 0.35$). Seventeen of the surviving, nonreversed patients had TG levels at the time of surgery, within the first post-operative year, and more than 20 years after operation (Fig. 3). Mean TG more than 20 years after surgery was

TABLE 5A. Plasma Triglyceride Results (mg/dL) in Long-term Survivors After Partial Ileal Bypass

Case	Baseline	Follow-up Interval (years)					
		1	2-5	6-10	11-15	16-20	>20
11	283		403	171			768
13			123	129			129
15			204	108			119
19	100		112	170			88
21	174	172	112				97
22			137	178	108		68
24	677	253	312			209	178
25		302	492				565
26	139	82	100				177
29	1632	1737	895	379	145		151
30	93	113	155				129
34	312	168					147
35	76	140	83				210
41		247					118
45	141	117		88	105		72
46	313		348				259
47	117	129	142	123	339	272	150
48	151	206					198
49	120	173	130				117
50	1524	966	1480				570
51	417	298	423	288			142
54	365	317	490	280	334		290
55	186	269	197	198	265	222	209
56	129	152	179				274
57	76	103	119				359

TABLE 5B. Plasma Triglyceride Results (mg/dL) in Nonsurvivors and Reversed Patients After Partial Ileal Bypass

Case	Baseline	Follow-up Interval (years)				
		1	2-5	6-10	11-15	16-18
1			375	179	160	
2			420	121	243	
3			177	196	181	60
4						
5			152	90		
6			254	520	85	315
7			206	147		
8						
9			75	87		
10			265	223		
12						
14						
16*			269			
17			239	119		
18						
20	328	344				
23	372	263		179	179	
27				126		
28				158		
31				224		
32			558	289	245	
33			160	327		
36	448		188	154	295	
37			321	360		
38			168	219		
39*	60		124	146		
40				258		
42			217	233		
43			95	66		
44			146			
52	782	478	269	450		
53	292		202			

* Partial ileal bypass reversed.

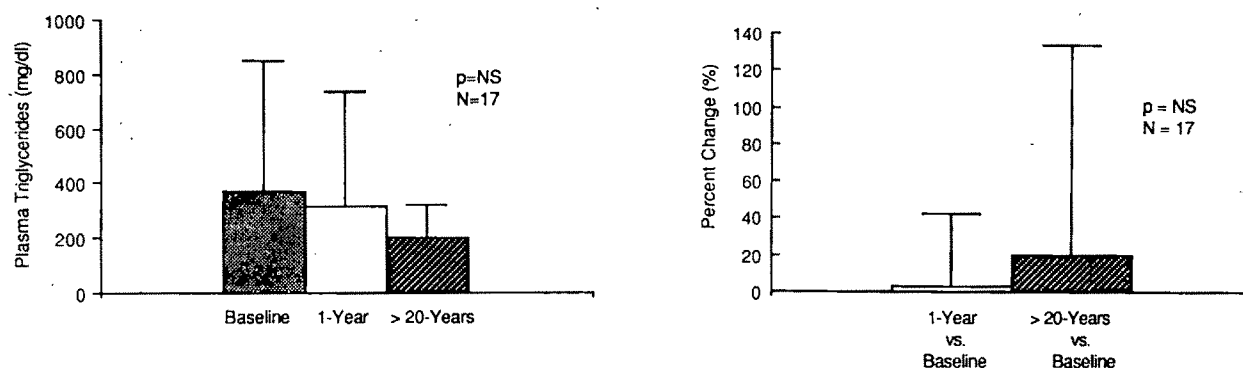


FIG. 3. Plasma triglyceride results (mean $\pm$ SD) and percentage changes from baseline (mean $\pm$ SD) in 17 patients with baseline, 1-year, and >20-year results after partial ileal bypass.

lower than either the preoperative level (372.3 ± 479.9 mg/dL versus 204.1 ± 119.0 mg/dL, $p = 0.14$) or the 1-year result (317.6 ± 418.1 mg/dL versus 204.1 ± 119.0 mg/dL, $p = 0.26$). The mean percentage changes between baseline and 1 year ($3.2\% \pm 39.3\%$, $p = 0.74$), between baseline and more than 20 years ($19.8\% \pm 114.4\%$, $p = 0.49$), and between 1 year and more than 20 years ($8.8\% \pm 79.9\%$, $p = 0.66$) also failed to achieve statistical significance.

To determine whether TG change within the first year of operation influenced long-term survival after PIB, the percentage changes between the preoperative and 1-year TG levels in long-term survivors ($3.2\% \pm 39.3\%$, $n = 17$) and in nonsurvivors ($-20.6\% \pm 29.2\%$, $n = 4$) were compared. The difference in the TG response within the first

postoperative year was not statistically significant ($p = 0.27$), although the number of determinations in non-survivors was limited.

The TG results within the first year and more than 20 years after PIB were assessed in terciles based on the preoperative TG level (Table 6). In patients with the lowest preoperative levels, mean TG tended to increase; whereas in patients with the highest preoperative TG levels, mean TG values decreased. The number of patients with elevated preoperative TG levels, however, was small.

In addition to TC and TG level determinations, a complete lipid profile was performed in the 25 surviving, non-reversed patients. More than 20 years after partial ileal bypass, HDL cholesterol was 45.4 ± 16.3 mg/dL, LDL cholesterol was 122.2 ± 50.4 mg/dL, VLDL cholesterol

TABLE 6. Plasma Triglyceride Results (mg/dL) After Partial Ileal Bypass by Preoperative Plasma Triglyceride Level

Patients with preoperative and 1-year results

	≤ 200 (n = 12)	201-600 (n = 7)	> 600 (n = 3)
Preoperative	121.8 ± 39.6	388.4 ± 61.3	1277.7 ± 523.0
1-year	148.3 ± 51.2	293.7 ± 104.1	985.3 ± 742.2
% change	28.5 ± 40.6	$-24.3 \pm 23.2^*$	$-30.9 \pm 34.9^*$

Patients with preoperative and > 20-year results

	≤ 200 (n = 12)	201-600 (n = 5)	> 600 (n = 3)
Preoperative	125.2 ± 35.4	338.0 ± 53.1	1277.7 ± 523.0
> 20-year	173.3 ± 83.6	321.2 ± 258.3	300.0 ± 234.5
% change	57.6 ± 117.3	2.9 ± 96.4	-75.7 ± 14.2

Patients with preoperative, 1-year, and > 20-year results

	≤ 200 (n = 11)	201-600 (n = 3)	> 600 (n = 3)
Preoperative	127.5 ± 36.2	364.7 ± 52.5	1277.7 ± 523.0
1-year	150.5 ± 53.1	261.0 ± 81.1	985.3 ± 742.2
% change vs. preoperative	21.4 ± 33.8	$-29.3 \pm 16.5^*$	$-30.9 \pm 34.9^*$
> 20-year	181.1 ± 83.0	193.0 ± 84.0	300.0 ± 234.5
% change vs. preoperative	63.9 ± 120.8	-46.5 ± 23.4	-75.7 ± 14.2
% change vs. 1-year	35.0 ± 87.2	-24.5 ± 24.2	-54.0 ± 32.8

* $p < 0.05$ vs. ≤ 200 mg/dL group.

was 50.2 ± 57.8 mg/dL, apolipoprotein A-I was 121.6 ± 38.6 mg/dL, and apolipoprotein B-100 was 96.6 ± 28.6 mg/dL.

In the surviving, nonreversed patients, nonatherosclerotic follow-up data were collected (Table 7). Excluding two reversed patients and two patients undergoing operation at the ages of 12 and 17 years, preoperative and follow-up weights more than 20 years after operation were available in 20 patients (three cases missing preoperative values). No significant change in weight after PIB was observed (72.8 ± 14.7 kg *versus* 68.1 ± 18.8 kg, $p = 0.21$). Six surviving patients (24%) reported 1 to 2, 13 patients (52%) reported 3 to 5, and 6 survivors (24%) reported more than 5 daily bowel movements. Only one patient required regular bowel-controlling medication, and no patient felt that bowel movement frequency necessitated a significant life-style modification. Six survivors (24%) experienced frequent postprandial bloating, and six patients reported excessive flatus. Eight patients required a cholecystectomy during the follow-up period; however the number of *in situ* gallbladders at the time of PIB could not be ascertained accurately from medical records or recalled by the patients with certainty. One patient was noted to have cirrhosis at the time of cholecystectomy. Ten patients (40%) developed nephrolithiasis, with two patients (8%) requiring operative stone removal. No kidney loss or decrease in renal function was reported. Two patients (8%) have undergone repeat operation for small bowel obstruction, and one patient (4%) has developed an incisional hernia. Three surviving patients have a diagnosed malignancy (1 prostate, 1 bladder, and 1 vocal cord), and 1 patient developed cataracts.

Clinically apparent atherosclerosis evolved in many of the surviving, nonreversed patients 20 or more years after PIB (Table 8). Sixty per cent of these patients have angina

TABLE 7. *Nonatherosclerotic Follow-up in 25 Surviving, Nonreversed Patients After Partial Ileal Bypass*

Weight change (kg) vs. preop. (n = 20)	-4.7 $\pm$ 16.3
Percentage change vs. preop.	-5.4 $\pm$ 21.7
Bowel movements per day	
0-2	6 (24)
3-5	13 (52)
>5	6 (24)
Requiring regular bowel-controlling agents	1 (4)
Gas-bloat symptoms	6 (24)
Excessive flatus	6 (24)
Cholecystectomy	8
Cirrhosis	1
Nephrolithiasis	10 (40)
Requiring operation for extraction	2 (8)
Small bowel obstruction requiring operation	2 (8)
Incisional hernia	1 (4)
Cataract development	1 (4)
Malignancy (1 prostate, 1 bladder, and 1 vocal cord)	3 (12)

Values in parentheses are percentages.

TABLE 8. *Atherosclerotic Cardiovascular Disease Follow-up in 25 Surviving, Nonreversed Patients After Partial Ileal Bypass*

Cardiac	
Angina requiring medical therapy	15 (60)
Myocardial infarction	4 (16)
Coronary artery bypass surgery	7 (28)
Peripheral vascular	
Claudication	4 (16)
Abdominal aortic aneurysm repair	2 (8)
Peripheral vascular bypass	2 (8)
Cerebral	
Transient ischemic attack	1 (4)
Stroke	3 (12)
Carotid endarterectomy	2 (8)

Values in parentheses are percentages.

requiring at least occasional pharmacologic treatment, 16% of the survivors have sustained at least one myocardial infarction, and 28% have undergone coronary artery bypass surgery. Four survivors (16%) have lower-extremity claudication and four patients (16%) have undergone either abdominal aortic aneurysm repair or bypass surgery to the lower-extremity vasculature. One patient (4%) reported transient ischemic attacks; three patients (12%) suffered strokes, and two patients (8%) underwent carotid endarterectomy.

Mortality results are summarized in Table 9. One patient died of a myocardial infarction on the fourth postoperative day (operative mortality rate = 1.8%) and two additional patients died within the first postoperative year. Coronary heart disease was the cause of death in 80% of cases. Three patients (10%) died as a consequence of malignancy (two breast and one lymphoma). In one patient the cause of death could not be determined by medical record review and was unknown to her surviving relatives. Overall actuarial survival rates were 94.7% at 1 year, 87.7% at 5 years, 74.9% at 10 years, 58.5% at 15 years, 53% at 20 years, and 40.8% at 25 years after PIB (Fig. 4).

Discussion

Coronary heart disease remains the most frequent cause of death in the United States and in the western world.⁶ In 1988 diseases of the heart accounted for 35.5% of all deaths in this country. Two thirds of these deaths were due to ischemic heart disease, the mortality rate (207.9 per 100,000) exceeding that observed in any other disease category, including all types of malignancy combined (198.6 per 100,000). Hypercholesterolemia clearly has been established as a major risk factor for the development of atherosclerosis and for death due to CHD.^{3,20} The screening results of the Multiple Risk Factor Intervention Trial demonstrated that asymptomatic adult men with total serum cholesterol levels equal to or greater than 264 mg/dL had a 6-year CHD mortality rate of 13.05 per 1000, which is 4.13 times the rate observed in patients with total serum cholesterol levels less than 167 mg/dL.^{5,21,22}

TABLE 9. Mortality Results in 57 Patients After Partial Ileal Bypass

30-day (operative) mortality	1 (1.8)
1-year mortality	3 (5.4)
Causes of death	
Coronary heart disease*	24 (42.1)
Ruptured abdominal aortic aneurysm	1 (1.8)
Ruptured cerebral aneurysm	1 (1.8)
Breast cancer	2 (3.5)
Lymphoma	1 (1.8)
Unknown	1 (1.8)
Total	30 (52.6)

Values in parentheses are percentages.

* Includes sudden death, myocardial infarction, and congestive heart failure.

Although the pantheon of lipid/atherosclerosis intervention trials using dietary or pharmacologic approaches to lower TC failed to demonstrate a beneficial effect of treatment on overall survival,²³⁻²⁶ aggressive TC reduction has been shown to decrease the rate of new coronary artery lesion formation and to retard the rate of existing lesion progression assessed angiographically.^{27,28} The incidence of clinical atherosclerosis events considered in combination, *i.e.*, CHD death or definite, nonfatal myocardial infarction, has also been reduced.²⁹ In the current clinical atmosphere, it appears prudent to advocate TC reduction in hypercholesterolemic patients, particularly in those with clinically evident atherosclerosis.

Beginning in 1962 experiments performed in our laboratory^{10,11,30} and by others,^{31,32} and retrospective analysis of patients undergoing ileal resections, demonstrated that both cholesterol and bile acid absorption from the intestine, and plasma cholesterol, were significantly

reduced, without concomitant weight loss, after diversion of substantial lengths of the distal small intestine. Although the entire small intestine is capable of cholesterol absorption, preferential cholesterol uptake occurs in the distal half of the small intestine. The absorption sites for bile acids are less well defined; however our experiments demonstrated that bypass of the distal one third of the small intestine significantly interferes with the enterohepatic bile acid circulation and leads to a threefold increase in fecal bile acid excretion.¹¹ Thus the metabolic basis for PIB was defined. Total plasma cholesterol reduction results from (1) a direct cholesterol drain from increased fecal loss of normally absorbed exogenous (dietary) and endogenous (biliary and intestinally secreted) cholesterol, and (2) an indirect cholesterol drain from increased hepatic conversion of body cholesterol stores to bile acids to replenish the depleted bile acid reservoir.

Partial ileal bypass was introduced clinically at the University of Minnesota in May 1963.¹² Radioisotope studies in volunteers after operation confirmed the mechanism by which the significant TC reduction accomplished by PIB occurs.^{33,34} Cholesterol absorption from the intestine was reduced by 60%. A 3.8-fold increase in total fecal steroid excretion occurred, with a 4.9-fold increase in bile acid excretion and a 2.9-fold increase in fecal neutral steroid losses. A compensatory 5.7-fold increase in the cholesterol synthesis rate developed. One year after surgery, the total exchangeable cholesterol pool was reduced by 33%, reflecting decreases in the freely miscible (plasma, red blood cells, liver, and intestinal mucosa) and in the less freely miscible (fat stores, muscle, solid organs, and vessel walls) cholesterol pools.

Since the introduction of PIB, more than 600 of these

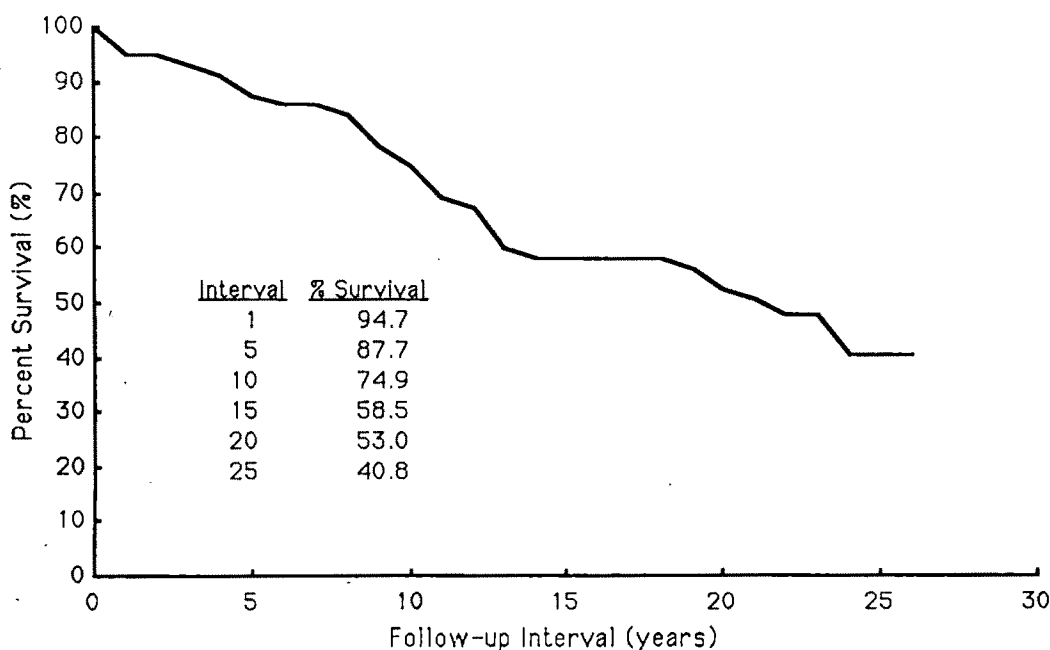


FIG. 4. Cumulative survival rates in the initial 57 hypercholesterolemic patients undergoing partial ileal bypass.

procedures have been performed at the University of Minnesota and at other centers in this country and worldwide.¹³⁻¹⁸ The largest experience with this operation is within POSCH, a randomized, prospective, multicenter, secondary intervention trial testing the therapeutic arm of the lipid/atherosclerosis relationship, with PIB as the intervention modality.¹⁹ The 5-year lipid results of PIB in 200 patients compared with those achieved by dietary fat and cholesterol restriction in 196 control patients have been published recently.³⁵⁻³⁷ In 1974 we reported 9-year lipid results in patients undergoing PIB outside of POSCH; however the number of patients with long-term follow-up was small.³⁸ The present analysis of 57 patients undergoing operation between 1963 and 1968 is the largest collected series of PIB patients available with follow-up of more than 10 years. In this series all patients were followed for a minimum of 20 years after surgery.

In these patients PIB led to 34%, 28%, 35%, 35%, and 30% reductions in TC levels 1 (n = 48), 2 to 5 (n = 49), 6 to 10 (n = 26), 11 to 15 (n = 11), and more than 20 years (n = 25), respectively, after operation. In 21 patients baseline, 1-year, and more-than-20-year TC levels were determined (Fig. 2). In these patients TC was 33% lower than baseline in the first postoperative year and remained 29% less than baseline more than 20 years after operation. No significant difference between the percentage reductions from baseline at 1 year and after more than 20 years was observed, demonstrating that the TC-lowering effect of PIB occurs within the first year of operation and is sustained, essentially unchanged, more than 20 years after surgery. This relationship was confirmed in the 17 patients with baseline, 1-year (-34%), 2- to 5-year (-23%), and more-than-20-year (-26%) TC levels; in the 8 patients with baseline, 1-year (-32%), 6- to 10-year (-34%), and more-than-20-year (-28%) TC levels, and in the 7 patients with baseline, 1-year (-30%), 2- to 5-year (-25%), 6- to 10-year (-34%), and more-than-20-year (-26%) TC levels.

The TC reduction achieved within the first year after PIB did not differentiate long-term survivors from non-survivors. Male and female patients achieved comparable TC reduction after PIB. Greater TC reduction was induced in patients with the most elevated preoperative TC levels (Table 3). The operation, however, appeared to be less effective in younger patients (age less than 30 years) than in older individuals. This may have been due to the inclusion of several younger patients afflicted with homozygous, familial hypercholesterolemia in this analysis. These patients, with severely elevated TC levels, responded poorly to PIB.

Plasma triglyceride levels were less frequently obtained and demonstrated considerable variability when available. Compared to the preoperative TG value, PIB led to a 2% increase at 1 year (n = 22), a 5% increase at 2 to 5 years

(n = 23), a 24% decrease at 6 to 10 years (n = 11), and a 23% increase in TG more than 20 years (n = 20) after surgery. None of these percentage changes from baseline were statistically significant. In the 17 patients with baseline, 1-year, and more-than-20-year TG determinations, PIB led to a 3% increase from baseline within the first year and a 20% increase from baseline more than 20 years after surgery. Both of these percentage changes from baseline were not statistically significant. Analysis of the TG response after PIB according to the preoperative TG value demonstrated that TG levels increased significantly within 1 year of operation and continued to be increased more than 20 years after surgery in patients with low to normal preoperative TG levels. The mean TG level after 20 years in this subgroup, however, continued to be less than 200 mg/dL. Similar TG increases have been noted during oral bile acid sequestrant therapy.³⁹ In patients with moderately and severely elevated preoperative TG values, PIB led to significant reductions within the first year and more than 20 years after surgery. More than 20 years after operation, the mean TG level in patients with moderately elevated baseline levels was below 200 mg/dL. In patients with severely elevated preoperative TG levels, the mean TG level more than 20 years after surgery was 300 mg/dL. The number of postoperative TG determinations in patients with abnormal preoperative TG levels was small. However these results suggest that increases in TG may not be a uniform consequence of PIB, and plasma triglycerides may actually decrease in certain subgroups after surgery.

The adverse effect profile of PIB has been a major factor limiting clinical acceptance of this procedure into the hypocholesterolemic armamentarium. More than 20 years after PIB, no significant change in weight was noted in the surviving, nonreversed patients, clearly differentiating this operation from the more extensive jejunoileal bypass (JIB) formerly used in the management of morbid obesity. Vitamin B₁₂ absorption is generally lost after PIB,⁴⁰ and all patients are advised to receive 1000 µg of vitamin B₁₂ intramuscularly every 6 to 8 weeks. Frequent bowel movements are the rule following PIB; however not one surviving patient felt that this required any significant lifestyle modification. One quarter of surviving, nonreversed patients had normal bowel habits, one half had between three and five bowel movements per day, and one quarter had more than five bowel movements per day. Only one patient was regularly taking medication to limit bowel movement frequency, and only one patient (1.8%) underwent reversal of his PIB due to intractable diarrhea. Cholelithiasis appears to develop at an increased rate after PIB, and removal of an *in situ* gallbladder should be considered at the time of operation. One patient was noted to have subclinical hepatic cirrhosis of unknown etiology, at the time of cholecystectomy. This patient continues to

be asymptomatic. Our experience would indicate that cirrhosis and hepatic failure, sometimes seen after JIB, do not occur after PIB.⁴¹ Nephrolithiasis occurs at an increased rate after bypass of the distal small intestine,⁴² and 40% of surviving, nonreversed patients in this series developed calcium oxalate renal calculi during the follow-up period. In the era preceding ultrasonic and endourologic techniques for noninvasive fragmentation and removal of stones, two patients (8%) required operation for stone extraction. No kidney loss or decrease in renal function has been noted in the surviving, nonreversed patients. One patient (1.8%) underwent PIB reversal for recurrent nephrolithiasis. Preventive treatment with a low oxalate diet, increased fluid intake, and oral calcium supplementation has not had an appreciable impact on the incidence of nephrolithiasis in these patients. The potential effect of urine alkalization with oral potassium citrate is undergoing prospective, randomized, placebo-controlled evaluation in members of the PIB group in POSCH. Finally an increased risk for the development of gastrointestinal malignancy has been a concern in patients after PIB due to the markedly increased bile acid load delivered to the colon. In more than 20 years of follow-up, no gastrointestinal cancer has developed in these patients.

Analysis of the atherosclerosis morbidity and overall mortality results reveals that despite highly significant, sustained, TC lowering, most surviving, nonreversed patients have developed clinically apparent atherosclerosis during the 20-to-26-year follow-up period, and CHD remains their most frequent cause of death. This raises the issue of whether any real benefit has been achieved by aggressive, surgically induced TC lowering in these patients and calls into question the value of any long-term treatment to reduce TC in hypercholesterolemic patients. The absence of a randomized control group in this series does not allow a definite response to this question. However observational epidemiologic data from the Framingham Study suggest that a 2% reduction in CHD mortality is achieved for each 1% reduction in the TC.⁴³ Thus, although the long-term CHD mortality rate in the patients reported is significant, a far greater CHD mortality risk can be hypothesized if no total plasma cholesterol reduction had been accomplished. Evidence supporting a reduction in this projected mortality rate may be found by comparing the survival rate in this patient population (Fig. 4) with the 5-year and the 15-year survival experience in the placebo-treated group participating in the Coronary Drug Project.⁴⁴ In these adult, male survivors of a myocardial infarction, with a mean total serum cholesterol of 249 mg/dL, the overall mortality rate without hypocholesterolemic therapy was 20.9% at 5 years and 58.2% at 15 years. In the present series, the mortality rate was 12.3% at 5 years and 41.5% at 15 years, 41% and 29% lower, respectively. Although the patient populations in these

two studies were dissimilar in mean TC levels and the prevalence of clinically apparent atherosclerosis at baseline, this comparison supports the hypothesis that intervention to reduce TC may have a beneficial impact on the course of CHD in hypercholesterolemic patients. Definitive evidence for such a conclusion, however, will be found in the results of prospective, randomized, controlled clinical trials, *e.g.*, POSCH, whose results will be available in October 1990.

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DISCUSSION

DR. ROGER GREENHALGH (London, England): This historical work we have heard from Dr. Buchwald is most courageous.

These patients were recruited during 1963 to 1968. It is well to recall the prevailing thought at the time. The aim was to lower cholesterol by a large amount and thus to bring about benefit in terms of arterial disease.

It was in the 1960s when the four major primary prevention studies for coronary artery disease were performed, and they showed collectively benefit from reduction of lipid levels in terms of development of the first cardiac event. In other words, for primary prevention there was benefit.

It was not until 1967 that Frederickson from the National Institutes of Health classified lipoproteins, and in 1969 Levy and Frederickson described the first controlled trial on angiographically documented coronary artery disease patients. They stressed the importance of the then so-called type II lipoprotein abnormality later referred to as type IIA.

In 1971, with Mr. Peter Martin and Dr. Barry Lewis, I described the first controlled trial of angiographically documented peripheral arterial disease patients in terms of banking serum lipid and lipoprotein levels.

It seemed at that time, 20 years ago, that it would only be a matter of time before the proof would be demonstrated of the value of the lipid lowering in terms of benefit for our vascular patients. But then one or two pieces of bad news followed.

The Coronary Drug Project showed negative results in many of the treatment groups. Then bad results were reported with atomids clofibrate. We knew this lowered fibrinogen and cholesterol and triglyceride, but the drug was discredited and withdrawn. Then in my own work in 1980 I was distressed to have to reveal that the lipid lowering conferred no benefit after arterial reconstruction whatsoever, but smoking was a factor that was of great importance.

More recently, in 1989 and 1990 from the femoropopliteal bypass study, a multicenter trial in the United Kingdom, we discovered that, for vein and prosthetic bypass, there was failure to demonstrate any relationship of cholesterol or triglyceride to outcome. The big factors were smoking and fibrinogen.

Therefore, back to the 1960s and the primary prevention situation and back to this paper, I wonder from these data, which are so valuable and have such an important place in history, whether the authors can give us any comfort that patients have had benefit from the primary prevention point of view, because we rather regret that from the secondary prevention point of view, lipid lowering at a rather late stage of the disease may have limited benefit.

DR. H. WILLIAM SCOTT, JR. (Nashville, Tennessee): In the early 1960s with Sam Stevenson and the help and strength of a large number of

residents and students working with us, we confirmed Buchwald and Varco's early reports of the cholesterol-lowering effects of distal small bowel bypass.

We also demonstrated in mongrel dogs and Rhesus monkeys on atherogenic diets with hypercholesterolemia and severe coronary and aortic atheroma in controls (slide) that total protection against both was afforded by distal intestinal bypass prior to starting the atherogenic diet. This slide shows a typical example of the data that we obtained in the control animals with severe atheroma after a period of 10 months in this monkey specimen, and the total lack of any atheroma or elevated serum cholesterol in the group of animals treated previously with distal intestinal bypass.

The further experiments that we carried out showed that, with intestinal bypass in monkeys operated on after 10 to 12 months on the atherogenic diet, the hypercholesterolemia returned to normal quickly; although when the diet was continued after the bypass, only partial but significant reduction in aorta atheroma was found at autopsy after 10 to 12 months.

I don't know if I made that clear: We started two groups of animals on atherogenic diet. At 10 to 12 months we killed one group of animals as controls for the degree of atheroma that we had to assume would be present in the test animals. The latter then were given distal intestinal bypass. We continued the diet for another 10 to 12 months, and then killed these animals.

They did not show the severe atheroma of the control animals. There was zero atheroma in two cases, and in the others, there were moderate to minimal degrees of atheroma, but much less than in the controls.

I have always regretted that we were not able to join with Dr. Buchwald in his important clinical study. We had to content ourselves with studies in obese patients with hyperlipidemia submitted to 80 to 90% intestinal bypass. In 193 of these patients followed up to 10 years, there were 99 with preoperative normal lipids and 94 others with hyperlipidemia. Both groups were treated with intestinal bypass of 80 to 90%, and in 19 type IIB patients by Frederickson's documentation, the cholesterol was reduced on the average by 59% of base and triglycerides by 63% of the baseline.

In 56 Frederickson's type IV patients, serum cholesterol dropped, on the average, 42% of base, and triglycerides on the average, 55% after bypass.

All of these patients, of course, had much more significantly elevated total cholesterol levels prior to the bypass.

There was only one patient in this group of 94 obese patients with hyperlipidemia who died with a myocardial infarction during a 5 to 10-year follow-up after a jejunoileal bypass. This was a 60-year-old man who died after resection of an atherosclerotic aortic aneurysm of a myocardial infarction some 4 years after his intestinal bypass.

Are your studies in your obese patients with hyperlipidemia similar to ours, and second, did the patients you reported today have documented myocardial infarcts prior to admission to their treatment study, as in the POSCH program that you are going to report on later this fall?

I have enjoyed this presentation very much, and I think these long-range results in your hyperlipidemic patients are certainly encouraging.

DR. WALLACE P. RITCHIE, JR. (Philadelphia, Pennsylvania): I have been associated with partial ileal bypass and the POSCH trial indirectly for almost 30 years. I was a resident when all but one of these cases were done at the University of Minnesota. I assisted on many. I did a few, and those are probably the ones that had the major complications in the postoperative period.

I also had the privilege of serving as an ad hoc member of the Clinical Trials Review Committee when the POSCH Project was debated, vociferously on occasion; at least twice, and I sat on the Study Section when it was truly peer reviewed, and I will say that it always received a highly enthusiastic reception and a very high prior score.

The POSCH trial is unique in that it is investigator initiated and grant funded; it is not institute initiated and contract funded, and the investigators are to be congratulated for carrying it through to its conclusion. We look forward to its end results.

I would echo the comments of the first commenter and ask Henry to comment on a couple of other aspects.

First the cholesterol-lowering effect is, indeed, impressive, and it is also obligatory, but (at least in the manuscript) there is an increase in the triglyceride levels from baseline of some 20-plus per cent, and some cardiologists would argue that the absolute levels of HDL achieved are not optimal or even comparable to what other regimens can achieve.

I agree that comparing the results here in terms of mortality on an annualized basis with the coronary artery project is comparing apples and oranges, but what about the Helsinki trial in which Gemfibrozil was evaluated? It has a lesser cholesterol-lowering effect than partial ileal bypass, but as I read the data, the annualized mortality of the trial you presented here is roughly comparable to that noted in the Helsinki study. Perhaps you could comment on that.

A 40% incidence in survivors of calcium oxalate stones is really quite remarkable and may have relevance to things far beyond partial ileal bypass: for example, patients with extensive ileal colonic Crohn's or ileal resections involving more than 100 cm. The conventional wisdom in gastroenterology is that this can be prevented by a low oxalate diet, but this does not seem to be the case with partial ileal bypass. Perhaps you could tell us why that might be the case.

Finally, I would be very interested to know what your bias is at present, if you can give it to us, as to where this operation really fits into the current therapy of this condition, particularly in view of the fact that we now have some remarkable drugs, such as Lovastatin, that can achieve a comparable degree of cholesterol lowering?

DR. H. J. SUGERMAN (Richmond, Virginia): Have you found decreased levels of vitamin B₁₂ or the fat-soluble vitamins (A, D, and E) in these patients? And have you noted any problem with osteoporosis that could occur from both hypovitaminosis D and/or calcium loss with this procedure?

DR. PAUL H. JORDAN (Houston, Texas): I would like to ask Dr. Buchwald, is the cholesterol lowering effect due to the decreased absorption of cholesterol, or is it due to the increase in the conversion of cholesterol to bile acids, which are then not reabsorbed because of the type of preparation that you have here?

I am reminded of an experiment that I was involved with in Dr. Bergstrom's laboratory, in 1958. The experiment was in rats, not man, I am sorry to say, but in prolonged biliary fistulas, which is comparable in some ways to the bypass, the cholesterol level fell a little bit, but stayed constant as if the liver just took over production and maintained a constant serum cholesterol level regardless of the amount of cholesterol that might have been lost in the conversion to bile acids.

DR. HENRY BUCHWALD (Closing discussion): Dr. Greenhalgh asked if cholesterol reduction is of any benefit in the primary prevention setting. I cannot provide a firm answer based on the current data. Only six or seven of these patients underwent operation in the primary prevention setting, that is, before evidence of atherosclerotic disease had developed. I would not, however, be as pessimistic as he is with respect to secondary prevention. The Cholesterol-Lowering Atherosclerosis Study (CLAS), although demonstrating no overall mortality benefit, did demonstrate less angiographic progression of atherosclerotic disease when total plasma cholesterol and LDL cholesterol levels were markedly reduced with combination colestipol/niacin treatment.

I would ask the audience to be patient and await the results of the Program on the Surgical Control of the Hyperlipidemias (POSCH) trial. This is probably the best secondary intervention trial that has been performed. We will not only have mortality and clinical event data, but we will also have sequential coronary arteriograms. We will have at least three follow-up arteriograms, over a 7- to 10-year follow-up period, in the survivors of the 838 patients in POSCH to compare with their pre-randomization study.

What can be concluded from the current data? One can only speculate; however, if you compare the survival experience of these patients with the survival reported in other studies, a 53% survival rate at 20 years compares quite favorably. There are very few studies in the lipid/atherosclerosis field with follow-up extending beyond 20 years.

I have been delighted to have Dr. Scott as a friend and as an encourager for all these many years since we first started working in the cholesterol field with partial ileal bypass. I would like to take this opportunity to thank him for his kind support and help. Dr. Scott, with regard to our results with the jejunoileal bypass: In a large series of patients undergoing this operation, a 40% reduction in the total plasma cholesterol level was observed. It is important not to measure the cholesterol level during a hypocaloric state. It must be measured in an isocaloric state, since any acute stress, such as starvation, pneumonia, and so on, will markedly

lower the total plasma cholesterol level. The patient population in the current study is quite similar to the POSCH population. Some of these patients were sicker and had sustained more than one myocardial infarction. The POSCH patients had survived a single myocardial infarction.

In response to Dr. Ritchie's inquiries, the importance of triglyceride increases remains unclear. Recently the Framingham Study demonstrated that triglycerides are not a primary atherosclerosis risk variable on the order of total plasma cholesterol, LDL cholesterol, or HDL cholesterol. In the patients in the present study, no overall change in triglyceride levels was seen. Many started with high triglycerides, and these were reduced. In those with low triglycerides, these levels tended to increase approximately 20%; however, they remained within, or only slightly above the normal limit. In the POSCH trial, there are very few hypertriglyceridemic patients. In POSCH, the overall increase in triglycerides is significant; however, again, these levels have remained within, or only slightly above the normal limit.

Regarding the HDL cholesterol response, partial ileal bypass in POSCH raised the HDL cholesterol level about 6%. This is somewhat less than the increase observed in the Helsinki Heart Study. At the same time, the LDL cholesterol lowering in the POSCH trial is nearly 40%, which is much greater than the LDL cholesterol lowering accomplished by gemfibrozil in the Helsinki Heart Study.

Nephrolithiasis is a significant, and probably the most significant, complication of partial ileal bypass. We have been unsuccessful in our attempts to manage this problem with dietary oxalate restriction, increases in oral fluid intake, or with oral calcium carbonate supplements to bind intestinal oxalate. Alkalization of the urine using potassium citrate is currently undergoing prospective, randomized, double-blind evaluation in the POSCH trial. There seems to have been a salutary effect; however, the final results are not yet available.

What will be the ultimate role of partial ileal bypass in the cholesterol-lowering armamentarium? I can only express my viewpoint that, in

comparison with all other modes of lipid-lowering therapy, partial ileal bypass is the most effective single modality, with the exception of lovastatin. Lovastatin has never been subjected to a phase-3 trial. This drug was released before long-term toxicity analyses had been performed in humans. I would hesitate and wait for a few years before encouraging all hypercholesterolemic patients to take lovastatin. In terms of a lasting effect, partial ileal bypass has a sustained hypocholesterolemic effect. This is not as clear with drug therapy. One reason that drug therapy may not have a lasting effect is that people do not take medications consistently over a prolonged period. An operative intervention, such as partial ileal bypass, is obligatory in its effect and is not dependent on patient compliance.

Dr. Sugerman, from the POSCH data, carotene levels are lowered following partial ileal bypass; however, vitamin A levels are normal. All patients are encouraged to take intramuscular vitamin B₁₂; however, some patients recover their intestinal vitamin B₁₂ absorptive capacity during follow-up. Vitamin D and E levels remain normal following partial ileal bypass, and we have not seen any evidence of osteoporosis.

Dr. Jordan, the mechanism of action of partial ileal bypass is twofold. Cholesterol is excreted in the stool, and this serves as a direct drain on the cholesterol pool. Bile acids are also lost in the stools, and this acts as an indirect drain forcing conversion of cholesterol to bile acids to replenish the depleted bile acid pool. In a sense, partial ileal bypass has double the effect of drugs, such as cholestyramine, that act only as bile acid-binding agents. Cholesterol synthesis increases following partial ileal bypass. The magnitude of this increase is species-dependent. The rat increases cholesterol synthesis to such a degree that the effect of a partial ileal bypass is negated. Fortunately, the human being is similar to a rabbit or to a swine, and does not increase cholesterol synthesis to such a magnitude. The net result of a partial ileal bypass in man is significant, sustained reduction of the plasma cholesterol pools, in addition to the total plasma cholesterol and the LDL cholesterol levels.

Effects of Aging on Duodenal Bicarbonate Secretion

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The incidence of duodenal ulcer increases with age, but acid secretion does not. We have investigated the effects of aging on a mechanism of duodenal mucosal defense. Basal and acid-stimulated bicarbonate secretions were measured in the proximal duodenum in anesthetized rats of three different age groups (3 months, 1 year, and 2 years). The proximal duodenum was cannulated *in situ* between two plastic tubes that extend downward from a titrating chamber, and bicarbonate secretion was measured by the method of Flemström et al. Although there was no significant difference in basal secretion among three groups, bicarbonate secretion in response to luminal acid (100 mmol/L [mM] HCl) was diminished in 1-year-old and 2-year-old rats (1-hour integrated bicarbonate secretion; 3 months = 5.8 ± 0.7 ; 1 year = $3.1 \pm 1.0^*$; 2 years = $2.0 \pm 0.7^*$). We also studied the effects of two mediators for acid-stimulated duodenal bicarbonate secretion, vasoactive intestinal polypeptide (VIP), and prostaglandin E₂ (PGE₂). Intravenous infusion of VIP (0.4, 4, 40 nmol/kg/hr) and intraluminal administration of PGE₂ (10^{-5} mol/L [molar] and 10^{-4} mol/L) induced duodenal bicarbonate secretion in a dose-dependent manner in all three groups, without significant difference between groups. These findings suggest that the release of mediator(s) in response to acid is decreased in the duodenum of the aging rats. The progressive breakdown in mucosal defense mechanisms with increasing age may explain, at least in part, the age-related increase of incidence of duodenal ulcer disease.

THE INCIDENCE OF duodenal ulcer increases with age.¹⁻³ Because there is no evidence of increased aggressiveness of acid peptic digestion with aging, we have investigated age-related changes in bicarbonate secretion from the duodenal mucosa, which is an important mucosal mechanism for defense against acid and pepsin.⁴ Mucosal bicarbonate secretion maintains the pH within the mucus gel on the mucosal surface of the duodenum at neutrality, even when the intraluminal pH of

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duodenum is as low as 1.5 to 2.0.⁴⁻⁷ Hydrogen ions within the lumen are removed from the proximal duodenum by neutralization by bicarbonate that originates from the duodenal surface epithelium (as well as by pancreaticobiliary bicarbonate secretion).^{8,9} Recent studies suggest that impaired duodenal mucosal secretion of bicarbonate is an important factor in the pathogenesis of duodenal ulcer.¹⁰⁻¹³

The mechanisms that govern mucosal bicarbonate secretion include neurohumoral factors^{9,14-16} and luminal acid.¹⁷⁻¹⁹ The ability of the mucosa to respond to acid seems very important in the maintenance of the surface pH gradient and in the protection of mucosa. Acid-stimulated bicarbonate secretion from the duodenal mucosa appears to be mediated by endogenous prostaglandins, vasoactive intestinal polypeptide (VIP), and possibly by nervous mechanisms.¹⁹⁻²⁶

Aging is known to be associated with secretory and morphologic changes in the gastrointestinal tract,²⁷⁻³¹ but the effect of aging on mucosal bicarbonate secretion has not been investigated previously. In the present study we measured basal and acid-stimulated bicarbonate secretion from the proximal duodenal mucosa in rats of three different age groups. The effects of mediators of acid-stimulated bicarbonate secretion, prostaglandin E₂ (PGE₂) and VIP, were examined in rats of the same different ages.

Materials and Methods

Male Fischer 344 rats (obtained from the National Institute of Aging, Bethesda, Maryland) of three different age groups (3 month, 1 year, and 2 years) were used in this study. Rats were fasted overnight in wire-bottom cages with free access to drinking water. Rats were anesthetized with an intraperitoneal injection of 1.0 to 1.2 g/kg urethane, and a tracheostomy was performed. Cannulas were placed into a jugular vein and a femoral artery for infusion of test agents, and for monitoring blood pressure. Normal saline was infused intravenously at 4 mL/kg/hr to prevent dehydration during the procedure. The abdomen was opened through an upper midline incision. The two plastic cannulas, which extend downward from a titrating cham-

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* $p < 0.05$ versus 3 months.

ber, were inserted into the first portion of the duodenum, which was then ligated around flanges on the tips of the proximal and distal to the tubes in such a manner as to provide an isolated segment of duodenum for study that was excluded from the presence of gastric juice and pancreaticobiliary secretions (Fig. 1). The intraluminal distance between the ends of the two tubes was 12 mm. The abdomen was closed with the titrating chamber clamped 5 cm above the anterior abdominal wall of the rats. The titrating chamber was filled with a luminal perfusate (10 mL of 154 mEq NaCl), which had been bubbled with 100% oxygen for at least 30 minutes before the experiment. The perfusate was circulated by constant-pressure gas lift (0.4 kg/cm²) of 100% oxygen, and was changed two or three times until it was clear. The temperature of the perfusate was maintained at 37°C by means of a warm-water jacket, and body temperature was maintained at 37 to 38°C by a heat lamp.

Bicarbonate secretion was measured every 15 minutes by titration of the perfusate to an end point of pH 7.6 with 25 mmol/L HCl, as measured by an autotitration pH stat system (Radiometer, Denmark). After a period of stabilization (usually 30 minutes to 1 hour), two consecutive basal values were obtained, and test agents were then administered.

Rats were excluded from the study if the mean arterial pressure was not maintained above 80 mmHg. Arterial blood samples (0.1 mL) were taken through arterial cannula at the beginning and at the end of experiment to check blood pH and HCO₃⁻. If these values were not in

TABLE 1. Basal and Acid-stimulated Bicarbonate Secretion in Three Age Groups

Time (minutes)	Bicarbonate secretion in three age groups (μEq/cm/hr)		
	3 month (n = 8)	1 year (n = 8)	2 years (n = 8)
Basal 1	10.18 ± 0.73	11.60 ± 1.56	11.27 ± 1.47
Basal 2	10.55 ± 1.04	12.30 ± 1.33	11.15 ± 1.48
15	18.91 ± 1.40	15.51 ± 1.86	14.31 ± 1.53
30	17.26 ± 1.84	15.96 ± 1.98	14.32 ± 1.56
45	14.44 ± 1.33	15.25 ± 2.59	12.30 ± 1.42
60	13.93 ± 1.52	13.50 ± 1.94	11.73 ± 1.12

the normal range (pH: 7.34 to 7.46; HCO₃⁻: 18 to 27 mmol/L), the rats were excluded.

To study the effect of luminal acid, the perfusate was replaced by 10 mL of 100 mmol/L HCl (with addition of 54 mmol/L NaCl to achieve isotonicity of the perfusate) for 5 minutes. At the end of this period, the acid was removed and the reservoir and the cannulated duodenal segment were washed with 15 mL of circulating perfusate five times in 10 minutes. After this, bicarbonate secretion was measured for another hour.

In the second experiment we studied the effect of VIP and PGE₂ on duodenal bicarbonate secretion. Vasoactive intestinal polypeptide in saline that contained 0.1% bovine serum albumin was infused intravenously at the rate of 0.4, 4, and 40 nmol/kg/hr (4 mL/kg/hr) for 15 minutes in a sequence of increasing molarity. Because topical (intraluminal) administration of PGE₂ is more effective than systemic administration,²⁶ we studied the effect of intraluminal infusion of PGE₂ on the secretion of duodenal bicarbonate. We compared two dosages of PGE₂ (10⁻⁵ mol/L and 10⁻⁴ mol/L) that were added individually to the perfusate.

Vasoactive intestinal polypeptide was purchased from Bachem Inc. (Torrance, CA) and all other chemicals from Sigma Chemical Co. (St. Louis, MO). Vasoactive intestinal polypeptide was dissolved in distilled water and PGE₂ was stored at -20°C and dissolved in 95% ethanol just before use. Statistical analysis was performed with Student's *t* test. Results are expressed as microequivalents of HCO₃⁻ per centimeter of duodenum per hour (μEq/cm/hr), and percentage of basal bicarbonate secretion.

Results

Twenty-two (of eighty-five) rats were excluded because of hypotension or because of failure to meet acid-base criteria. Basal and acid-stimulated bicarbonate secretion in the three groups are shown in Table 1. There was no significant difference in basal bicarbonate secretion among the three groups. Perfusion of the proximal duodenum with 100 mmol/L HCl significantly stimulated duodenal

In vivo Measurement of Duodenal Bicarbonate Secretion in Rat

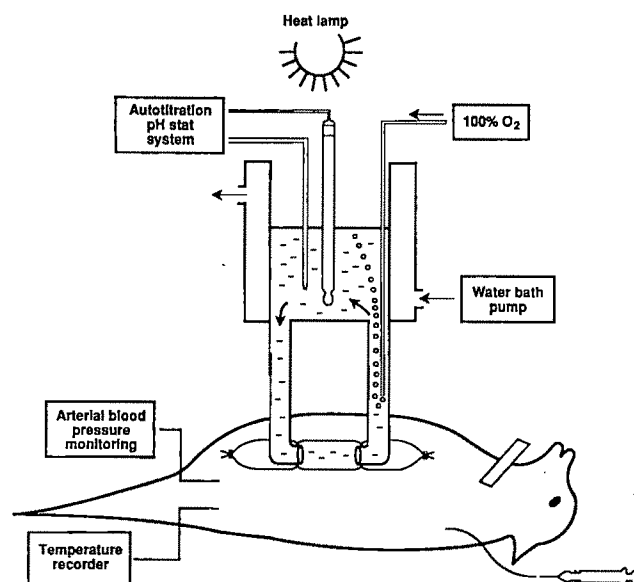


FIG. 1. Diagram of *in vivo* system for measuring duodenal bicarbonate secretion in the rat (modified from Flemström et al., 1982¹⁴).

bicarbonate secretion above basal for the entire hour in the 3-month-old rats. The peak bicarbonate output was increased by almost two times over basal. However bicarbonate secretion was weakly stimulated by luminal acid in the 1- and 2-year-old rats; the 1-hour integrated bicarbonate secretions after exposure to luminal acid were calculated and are shown in Figure 2. The response to acid was significantly less in 1-year and 2-year-old rats when compared to the 3-month-old rats. There was no significant difference between the HCO_3^- outputs of the 1- and 2-year-old rats.

Although the intraluminal distance between the ends of the two tubes of the reservoir and the length of test segment of duodenum was fixed at 12 mm in all rats, different-sized rats may have different diameter or surface area of duodenal mucosa. Therefore we examined our data expressed as percentage of basal secretion to compare the data from rats of different ages and sizes. The mean of two basal values of each rat was expressed as 100% basal output and the percentage bicarbonate output was calculated and shown at different times over the course of the experiment in Figure 3. Exposure of duodenum to luminal acid produced an immediate significant increase in bicarbonate output in all three groups. In young rats bicarbonate output was increased by 85.8% and 66.1% during the first and second 15 minutes after acidification, whereas in 1- and 2-year-old rats, it was increased by 33.6% to 39.2% during the same periods. Furthermore, in the young rats, acid-stimulated bicarbonate output remained

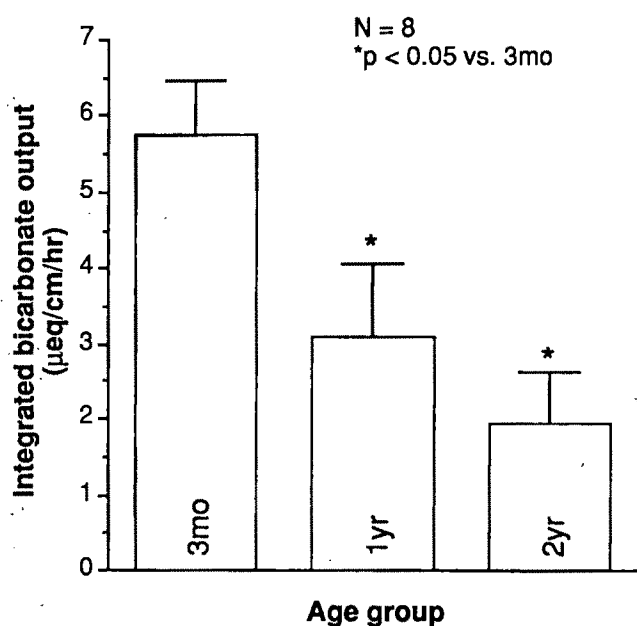


FIG. 2. Effect of luminal acid (100 mmol/L HCl) on duodenal bicarbonate secretion in rats of three age groups. Results in this figure are 1-hour integrated values and expressed as mean $\pm$ SEM. * = $p < 0.05$ vs. 3-month-old rats.

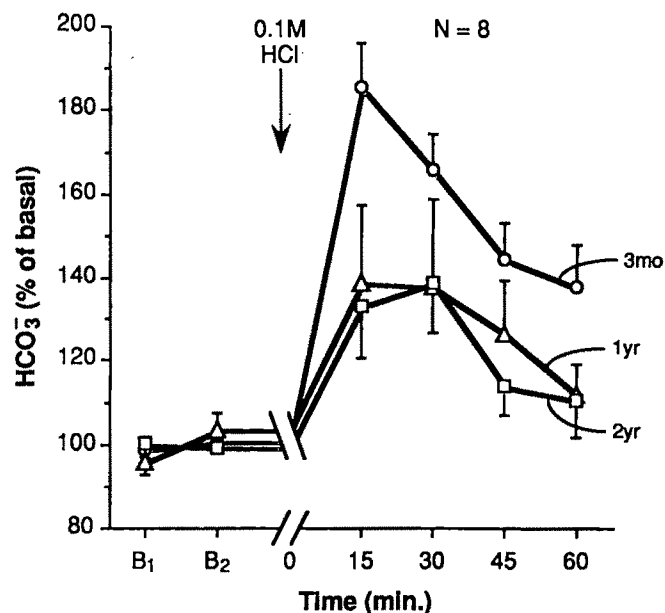


FIG. 3. Effect of luminal HCl (100 mmol/L) on bicarbonate secretion from proximal duodenum in three age groups (3 months, open circle; 1 year, open triangle; 2 years, open square). The results are expressed as percentage of basal secretion. Number of rats of each group is eight and mean $\pm$ SEM are shown.

above basal for at least 1 hour, whereas in 1- and 2-year-old rats bicarbonate returned to near-basal levels after only 30 minutes.

Intravenous infusion of VIP increased duodenal bicarbonate secretion in a dose-dependent manner in all three groups (Fig. 4). All three groups responded well to two higher doses of peptide without difference between groups. Bicarbonate secretion was increased three times during infusion with VIP 40 nmol/kg/hr, and this was greater than that achieved by 100 mmol/L HCl stimulation. Similarly the response to both doses of PGE₂ was similar in the three age groups (Fig. 5). In the 3-month-old rat, the bicarbonate output during 10^{-4} mol/L PGE₂ stimulation was similar to the peak output in response to 100 mmol/L HCl.

Discussion

Although many consider peptic ulcers a disease of middle age, this concept is based on the number rather than on the rate of ulcer patients. Most epidemiologic studies have not used strict criteria in determining the ulcer-incidence rate, which is defined as the number of new cases arising during a given time interval per specified unit of population.^{32,33} The well-designed studies of ulcer incidence by Bonnevie^{1,2} in Denmark and by Kurata and colleagues³ in the United States have demonstrated that the age-specific incidences of gastric ulcer and duodenal ulcer increase in an almost linear manner in men and women from the age of 15 to 80. On the other hand, basal

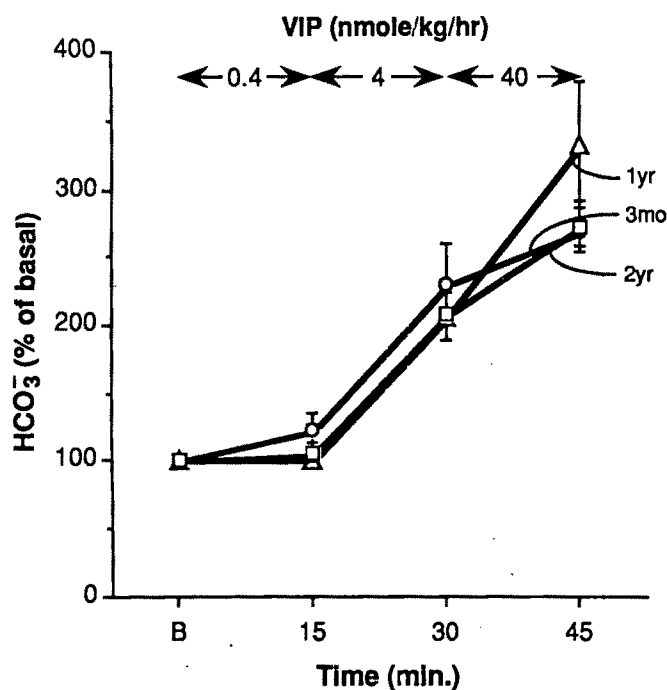


FIG. 4. Duodenal bicarbonate secretion in response to VIP. Vasoactive intestinal polypeptide was infused intravenously at a rate of 0.4, 4, 40 nmol/kg/hr serially. All three groups responded in a similar manner. Mean $\pm$ SEM are shown and number of rats for each group is six (open circle, 3 months; open triangle, 1 year; open square, 2-year-old group).

and stimulated gastric acid secretions is decreased progressively with aging in humans²⁷⁻²⁹ and in rats.³⁰ Therefore the higher incidence of peptic ulcer disease in the aging population, despite a decreased secretion of acid, suggests that factors concerned with mucosal defense may be relatively more important in the pathogenesis of duodenal ulcer in the elderly.

The secretion of bicarbonate and mucus in the duodenum is the main defense mechanism against acid.⁴ Mucus adherent to the luminal surface of the mucosa provides a zone of low turbulence (so-called unstirred layer), allowing the development of a gradient for HCO_3^- from the mucosal side and H^+ from the luminal side.³⁴ Small amounts of bicarbonate protect the mucosa against large amounts of acid by neutralizing H^+ ions that diffuse back into the mucus layer. Impaired duodenal bicarbonate secretion is thought to play an important role in the pathogenesis of experimental¹⁰⁻¹² and clinical¹³ duodenal ulcer disease. Isenberg and colleagues¹³ have reported recently that patients with inactive duodenal ulcers have decreased production of bicarbonate, both basal and acid-stimulated, in the mucosa of the proximal duodenum.

Acid is the major physiologic stimulant of bicarbonate secretion.¹⁷⁻¹⁹ Vasoactive intestinal polypeptide and endogenous prostaglandins are involved in mediating acid-stimulated bicarbonate secretion,^{15,17-19} but a role for mediation *via* other neurohumoral pathways has not been

clearly demonstrated.^{35,36} Vasoactive intestinal polypeptide is the most likely humoral factor mediating the bicarbonate secretory response to acid because it is a potent stimulant of duodenal bicarbonate response²⁰ and is released from nerve endings during the exposure of duodenal mucosa to acid.^{37,38} Algazi and colleagues²² found that the VIP antagonist ([4C1-D-Phe⁶, Leu¹⁷] VIP) inhibited duodenal bicarbonate secretion stimulated by luminal acidification. Stimulation of bicarbonate secretion is an important action of PGE₂.³⁹ Exposure of the duodenum to acid stimulates release of PGE₂ from duodenal mucosa,^{14,19} and acid-induced bicarbonate secretion is blocked by indomethacin.²⁵

Our study indicates that there is an age-related decrease in bicarbonate secretion stimulated by exposure of the duodenal mucosa to acid. We do not know whether this finding can be applied to humans. 'Old' animals are defined as having achieved the age at which one half of the population ordinarily dies (median survival time).^{40,41} That age in humans is about the eighth decade of life and in Fischer 344 rats the age is 23 to 26 months.⁴² Although the exact corresponding age of humans cannot be matched with that of rats used in the present study, our results obtained from three different age groups clearly reflect an age-related change and suggest a progressive breakdown in mucosal defense mechanisms in the proximal duodenum with increasing age. If similar changes are found

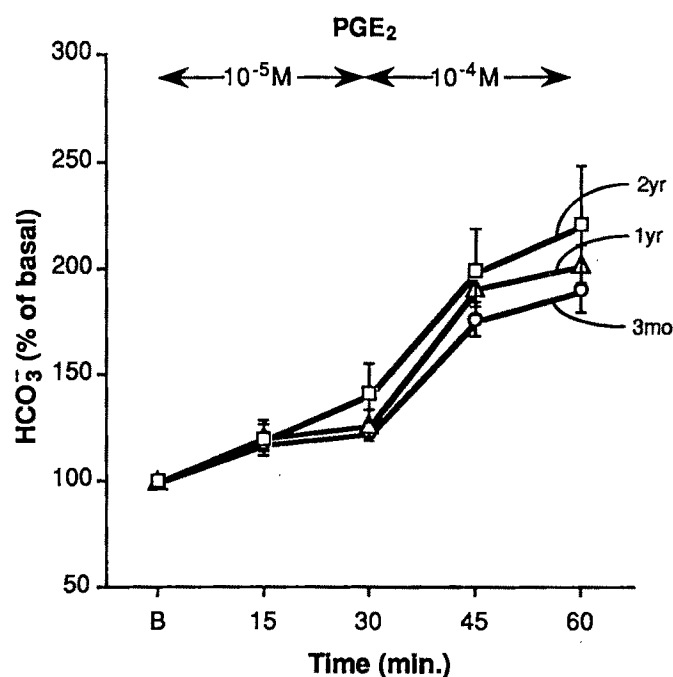


FIG. 5. Duodenal bicarbonate secretion in response to luminal PGE₂. Two different concentrations of PGE₂ (10^{-5} mol/L and 10^{-4} mol/L) in the perfusate were tested by adding PGE₂ solution to circulating perfusate. Mean $\pm$ SEM are shown. No difference between groups is noted. Open circle, 3 months ($n = 6$); open triangle, 1 year ($n = 9$); open square, 2-year-old group ($n = 6$).

in humans, this breakdown may explain, at least in part, the age-related increase in the clinical incidence of duodenal ulcer. Age-related changes in other mucosal defense mechanisms in the gastroduodenal region, including mucus secretion, mucosal blood flow, and rapid epithelization after mucosal injury also require investigation.

Hemodynamic and acid-base status influence duodenal mucosal bicarbonate secretion.^{43,44} Metabolic alkalosis, expansion of systemic blood volume, and increased mucosal blood flow may lead to a significant increase in bicarbonate secretion, whereas metabolic acidosis, shock, and decreased mucosal blood flow may reduce secretion. The network of microscopic blood vessels in the mucosa is deficient in the aged rat stomach.⁴⁵ Because aged rats may be more sensitive to systemic changes induced by our experimental procedures (including anesthesia and operation), pH and blood pressure were monitored during the experiment; 22 of 85 rats were excluded at the time of the experiment because of hypotension or abnormal acid-base balance. Twenty per cent of young rats (5 of 25), 23% (7 of 30) of 1-year-old rats and 33% (10 of 30) of 2-year-old rats were excluded.

We have demonstrated that duodenal bicarbonate secretion in response to VIP and PGE₂ is intact in 1- and 2-year-old rats, at least in the range of doses tested here. Because VIP and PGE₂ appear to be important physiologic mediators of acid-induced bicarbonate secretion, the results suggest that secretory potential of aged duodenal mucosa for bicarbonate is preserved and that the decrease in acid-stimulated bicarbonate secretion found with aging is due to decreased sensitivity of the mucosa to luminal acid or to decreased release of mediators in response to acid. It is unlikely that differences in blood flow or general condition of the rats in different age groups influenced the results as the diminution in bicarbonate secretion was in response to acid only, while the secretion in response to VIP and PGE₂ was preserved. A decrease in the number of neuropeptide-containing nerve fibers (substance P, VIP, somatostatin) in the small intestine has been reported in senescent rats (RLEF/LATI female rats, 36 months old).⁴⁶ We plan to determine whether acid-stimulated VIP release and endogenous PGE₂ production and release by the duodenal mucosa are disturbed with aging.

Basal and stimulated bicarbonate secretion from the proximal duodenal mucosa were measured in anesthetized rats of different ages. Although there was no difference in basal secretion, acid-stimulated secretion was decreased with increasing age. Vasoactive intestinal polypeptide and PGE₂ increased duodenal bicarbonate secretion in all three groups in a similar manner. The present study provides support for the concept that the increasing incidence of duodenal ulcer disease with aging may be caused, at least in part, by a progressive breakdown of the mucosal defensive response to acid in the proximal duodenum.

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DISCUSSION

DR. WILLIAM SILEN (Boston, Massachusetts): It was only about 10 years ago that it was recognized almost simultaneously in two laboratories, one in Sweden by Gunnar Flemström and in our own laboratory, that the duodenal mucosa alone, quite independent of bile and pancreatic juice, is capable of secreting large quantities of alkaline juice.

In some systems stimulated alkaline secretion by the duodenal mucosa comes close to approximating maximal acid output by the stomach. This alkaline secretion is most profound in the first 2 or 3 cm in the duodenum, decreases rapidly as one progresses distally and is not produced by Brunner's glands.

It has been demonstrated to occur in the human duodenum, and it has been shown to be reduced in at least one study in humans with duodenal ulcer.

Duodenal alkaline secretion probably is the most important mechanism in the duodenal mucosa as a protective mechanism aside from the inherent capability of that mucosa to rapidly reconstitute its integrity when injured.

Whereas for years we have focused our attention on the injurious properties of gastric acid, now we must direct our attention to the protective mechanisms. We and others have shown that nonsteroidal anti-inflammatory drugs can reduce this alkaline secretion, and we are indebted to Dr. Kim and his colleagues for calling to our attention the possibility that another factor such as age might also interfere with this important mechanism.

As surgeons who manipulate this area to a fairly considerable degree, we need to look forward to recognizing other factors that influence duodenal alkaline secretion.

I have one question of Dr. Kim and that relates to whether the acid that was instilled into the duodenum causes an injury. In some species 100 mmol/L acid will indeed do that, and I think Kim and associates need to exclude that possibility here because the appearance of alkaline secretion in the duodenum, while it is mainly an active transport, may occur under injurious circumstances by passive diffusion. The authors

would need to eliminate that as part of this response that they have shown.

DR. FRANK G. MOODY (Houston, Texas): The experiments of Dr. Kim and his associates were well conceived and presented and relate to what is being found in very carefully performed epidemiologic studies of ulcer disease. For example, in Sheffield in the United Kingdom, there has been a population-corrected, increased incidence of admission of older people to their hospital district with ulcer disease complicated by perforation and hemorrhage.

I do not know how old a 2-year rat is. Possibly the author can tell us, but it is known that as people get older, they have less acid secretion. Is it possible also in the rat that there is less acid secretion, leading to either stimulation or inhibition of the generation of prostanoids or VIP? Have you measured the tissue level of either of these agonists of bicarbonate secretion?

DR. DAVID FROMM (Detroit, Michigan): A component of alkali secretion is related to capillary filtration of bicarbonate. This then raises the question: Is there a difference in hemodynamic response of a 3-month-old as opposed to a 1-year-old rat?

Do the authors have any blood flow data in terms of age?

DR. JOSEF E. FISCHER (Cincinnati, Ohio): This is an elegantly simple and beautifully designed experiment, which tends to address the paradox of increased ulcer occurrence in the face of declining acid. What they find briefly is a decreased not only volume of response but also duration of response and with duodenal installation of acid; in the face of a preserved response to PGE₂ and, at least to my reading, in the upper two dosage range of VIP.

I don't know whether I am reading too much into the flat response in the 1-year-old and the 2-year-old rats to the lowest dose of VIP for micromoles per kilogram per hour, but it seemed to me that there was

a clear differential between the two older rats, which did not respond, and the younger rats, which did.

In the manuscript, which Dr. Thompson was kind enough to give me, they speculate on whether or not the difference between older and younger rats is due to decreased sensitivity or decreased release of mediators, and from the manuscript, it is obvious that they are also working on the nature of VIP and its response as a mediator.

I wonder whether or not the use of some VIP antagonists, which are now available in submaximal doses, would perhaps be useful in clarifying whether or not the neurocrine, or at least the paracrine, effects of VIP are really responsible as the mediator, and one could differentiate the mechanism on this basis, and if so, do they have any data to this effect? Thank you.

DR. SUNWHE KIM (Closing discussion): Dr. Silen asked about the possibility of mucosal injury with 0.1 M HCl. We don't know whether the duodenal mucosa was damaged by acid in our experimental system because we didn't examine the duodenal segment microscopically. 0.1 M HCl (isotonic by addition of NaCl) is below pH 2, which is very rare in both normal and duodenal ulcer patients. However, since the concentration of parietal secretion is 145 mM and gastric luminal pH can reach as low as pH 1.4, we believe that it is important to determine the response to such a high concentration of acid. We will check to see whether acid causes mucosal injury in our model and if there is any difference in magnitude among different age groups.

To answer Dr. Moody's question, we are planning to study the age-

related changes of the tissue content of VIP and PGE₂ in the duodenum. Although the decreased VIP content in the bowel wall of the aged rat has been shown in one report, this result is not applicable to our study because they used both different species and different age groups than we did. Regarding the corresponding ages of human, as compared with rats, I think it is very difficult to define the absolute corresponding age. According to the median survival time, I would think that three different age groups of rat are corresponding to young adult (20 to 30 years of age), adult (40 to 50 years), and the aged (60 to 70 years), respectively.

Dr. Fromm asked whether there were any differences in hemodynamic measurements during experiments among different age groups, differences that might have affected the bicarbonate secretion. The aged rats were excluded from the study more than younger rats because of hypotension, sometimes caused by minor bleeding or because of anesthesia that was a little too deep. Because all the rats with unstable hemodynamic status were excluded and responses to VIP and PGE₂ were well preserved in the aged rats, it is unlikely the hemodynamic condition contributed to the different responses to acid. However, if there is any change in the mucosal blood flow with age, it may well be one of the possible contributing factors.

Dr. Fischer pointed out the different pattern of response to VIP among age groups. We have noted these differences, but they were not statistically significant. If we add to the number of rats, it may turn out to be significant. With regard to the VIP antagonist, because the VIP antagonist is known to inhibit the acid-stimulated bicarbonate secretion, it would be very interesting to try this antagonist and to see how differently they respond.

An Electric Artificial Heart for Clinical Use

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Advances in microelectronics, high-strength magnets, and control system design now make replacement of the heart using an implantable, electrically powered pump feasible. The device described herein is a compact, dual pusher plate unit with valved polyurethane sac-type ventricles positioned at either end. The power unit consists of a small, brushless direct current motor and a motion translator. A microprocessor control system is used to regulate heart beat rate and provide left-right output balance. Bench studies lasting for as long as 1 year have been performed. Heart replacement with the electric heart has been performed in 18 calves since 1984. The longest survivor lived for more than 7 months. Among the causes of termination were component failure, thromboembolic complications, and bleeding. No major problem has been identified that precludes prolonged use of the electric heart. In the future the patient with end-stage heart disease will have an electric artificial heart as one therapeutic option.

CARDIAC TRANSPLANTATION HAS provided a new outlook for many patients with end-stage heart disease. However cardiac transplantation is not readily available to all of these patients. The number of donor hearts is limited and thus many patients die while waiting for a donor heart. Other patients have concurrent disease that excludes them from the candidate list, frequently because of the associated need for immunosuppressive therapy.

The possibility of heart replacement with a human-made device was seriously considered by Kolff and Akutsu¹ in 1958. The first such hearts to be successfully used in experimental animals were pneumatically powered pumps.² In 1982 DeVries and colleagues³ startled the medical world by electively implanting a pneumatically powered heart in the chest of a 62-year-old man with an end-stage cardiomyopathy. The results encouraged DeVries to implant a similar heart in three other patients, one of whom lived for more than 2 years. However inherent problems with the pneumatic heart (*i.e.*, the need for two tubes to pass through the body wall and the bulky pneumatic power unit) have shifted the focus of the permanent artificial heart to devices that do not require per-

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cutaneous tubes and that have smaller external components. This report describes the design and evaluation of an electrically powered artificial heart under development by our group.

Materials and Methods

The electrically powered heart consists of two pusher plate-activated blood pumps positioned on either side of a motor-motion translator assembly.^{4,5} Each blood pump is comprised of a very smooth segmented polyurethane sac positioned within a rigid polysulfone housing. Each sac is actuated by a pusher plate. Bjork-Shiley valves (Shiley Laboratories, Inc., Irvine, CA) with Delrin (E.I. DuPont de Nemours Co., Wilmington, DE) discs are secured at the inlet and outlet ports of each pump. The dynamic stroke volume of the pump is 90 ± 5 mL with a maximum output of 12 L per minute. Pusher-plate motion is produced by a brushless DC motor acting through a drum cam (initial version used in 10 calves) or a planetary roller screw (current version used in eight calves). The inlet and outlet ports of the pumps are connected to the respective atria and arteries using filler free silicone rubber-coated Dacron (DuPont) fabric sewing cuffs. The roller-screw electric heart is shown in Figure 1.

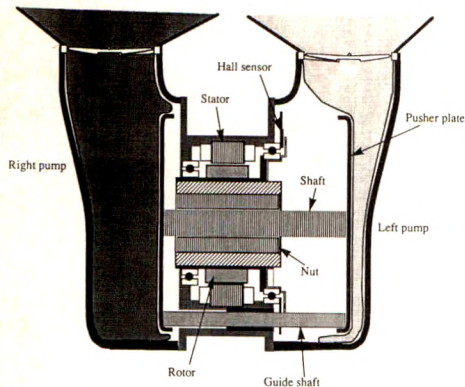
Electric energy is transmitted to the motor through an inductive coupling technique, which eliminates the need for any tube or wire to cross the skin. The primary (external) coil is energized at 155 kHz using house current or a portable battery pack. Energy is transmitted across the skin to the secondary (subcutaneous) coil with a 70% coupling efficiency.⁶ The energy is supplied to the motor controller. Information regarding the relative position of the rotor and stator are provided to the controller from Hall effect sensors (Microswitch, Division of Honeywell, Inc., Freeport, IL) on the motor case and a series of ultra-high-strength magnets attached to the rotor. In the roller-screw unit, a full stroke (2.5 cm) is provided by 63 revolutions of the nut, first turning in a clockwise and then in a counterclockwise direction. In addition to providing energy for the motor and controller, the secondary coil provides energy to charge an implantable battery capable of supporting pump function for as long as 20 minutes

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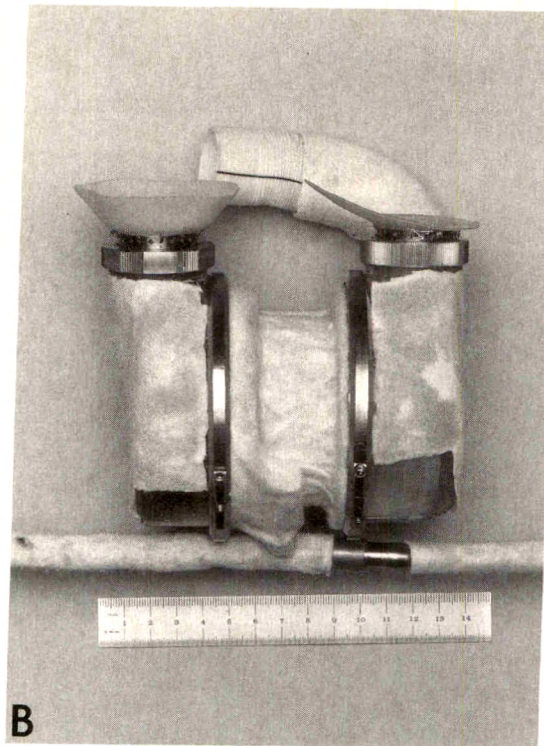
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A



B

FIGS. 1A and 1B. (A) A cross-section of the electric heart shows the electric motor (rotor and stator), roller screw (shaft and nut), two pusher plates, and the two blood pumps. (B) A photograph of the electric heart. The overall length is 11 cm, height is 10 cm, and the weight is 900 g. The central section of the heart is fabricated of a titanium alloy, while the pump cases are made of transparent polysulfone.

while the primary coil is temporarily removed or dislodged.

An electronic control system is used to balance the output of the right and left ventricles and to ensure adequate cardiac output.^{7,8} We have extensive experience with the use of automatic control of a pneumatic artificial heart in animals and in humans. With the pneumatic system, the left pump output is increased as arterial pressure decreases to less than its baseline value. The right pump output maintains the left atrial pressure at a normal preset range. This system has been modified for use with the electric heart in which both ventricle beat rates are equal but phase shifted by 180 degrees. Detailed bench studies using the electric heart have shown that the motor torque during left pump systole is related to the arterial pressure, so this value is used in the control scheme. Left atrial pressure is indirectly measured by determining the position at which the left pusher plate contacts the blood sac. Thus both of these key parameters (arterial and left atrial pressure) are indirectly measured without the use of pressure transducers and their attendant problems of temperature sensitivity and temporal drift.

The implanted artificial heart contains a relatively fixed gas volume within the motor and pump unit. To achieve effective output balance, the stroke volume of either ventricle must change independently of the other. Because of the fixed volume of gas within the motor space, this change in stroke alters the gas pressure, which can alter the stroke of the opposite ventricle. Accordingly a volume-compensation device or a compliance chamber is a re-

quired component of an artificial heart of this design.⁹ The compliance chamber is a $10 \times 15 \times 1$ cm segmented polyurethane chamber having a Dacron (DuPont) velour outer cover and is connected to the motor space. In animal implants it is positioned in the right pleural space. Because gasses slowly diffuse across polyurethane membranes, a compliance chamber access port is positioned in the subcutaneous position to allow replenishment of gas lost to diffusion across the polymer.

The mechanical heart has undergone extensive bench and mock loop testing. Each ventricle can pump from 6 to 12 L per minute at physiologic inlet and outlet pressures. The control system can handle perturbations in systemic and pulmonary resistances and has proved stable. Power consumption at nominal flow rates of 5 to 10 L per minute, a mean aortic pressure of 90 mmHg, and physiologic left atrial pressures ranged from 6.5 to 17 watts.¹⁰ Overall system efficiency using the wireless energy transmission system ranged from 16.1% to 20.9%. The longest period of continuous function on the mock circulatory loop has been 1 year.

Animal implant studies have been performed using 125-kg calves. A right thoracotomy was performed and conventional cardiopulmonary bypass was begun, removing blood from the caeve and pumping blood into the retrograde cannulated right common carotid artery. The heart was removed and atrial and arterial cuffs were doubly sutured with 4-0 polypropylene suture. Because of the mismatch in length-to-width ratio of the pump and chest dimensions, we developed a technique in which the pumps

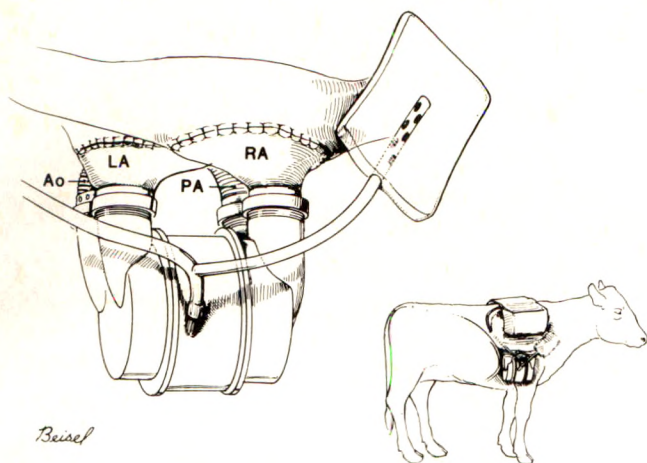


FIG. 2. This diagram shows the location of the heart in the experimental calf. The heart is positioned in the orthotopic location. The compliance chamber is placed in the right pleural space. Ao, aorta; PA, pulmonary artery; LA, left atrium; RA, right atrium.

are positioned in the calf with the long axis parallel to the sternum (Fig. 2). The quick connects were attached and air was removed from the pump. The heart was slowly energized as cardiopulmonary bypass was discontinued. Protamine was administered after removal of the cannulae. The compliance sac was positioned in the right hemithorax and the chest was closed. (While the wireless energy transmission system has been extensively evaluated on the laboratory bench and in animal studies with electric ventricular assist devices, to date only a hard wired system has been used with heart replacement in the calf.)

Each calf was placed in the recovery room in a cage and was extubated when the arterial blood gasses were adequate. After several days monitoring catheters and intravenous cannulas were removed. Each calf was given warfarin sodium to maintain a prothrombin value of 1.5 to 2 times control value. Pump parameters were monitored periodically. The animal was given a normal diet and water *ad libitum*. The calf was exercised on a treadmill at prescribed intervals.

An animal experiment was terminated if the animal became ill and could not be readily treated or if mechanical failure occurred. A complete necropsy was performed and the artificial heart was removed, disassembled, and thoroughly inspected. Where indicated, required modifications were incorporated in subsequent artificial hearts.

Results

Beginning in December 1982, 10 animals underwent implantation of the cam-type artificial hearts.¹¹ Two animals died within the first week of perioperative problems. The remaining eight calves lived from 9 to 222 days (mean, 50 ± 25 days). The causes of death were electro-

mechanical component failure (4), bleeding (2) thromboembolic (1), and undetermined (1).

With improvement in the roller-screw motion design heart (smaller size, less weight, improved mechanical reliability), we discontinued development of the cam unit. Since April 1986, eight calves have undergone heart replacement with the roller-screw unit. One animal died in the perioperative period. Seven animals lived from 9 to 170 days (ongoing), with an average survival time of 76 ± 23 SEM days (Fig. 3). Causes of death were electromechanical component failure (3), thromboembolic (2), and parasitic disease (1).

Discussion

Some of the earliest artificial hearts conceived in the 1960s were designs in which brush-type DC electric motors served as the prime movers.^{12,13} Those hearts were generally based on positive-displacement pumps that required an available volume of atrial blood to permit obligatory filling during diastole. If an adequate volume of atrial blood was not available, high suction pressures resulted in disastrous consequences. Brush wear was a potential, but often unrealized, problem. In pneumatic pumps filling is controlled by a gentle vacuum rather and is not obligatory. As a result most artificial heart progress in the 1970s was made with pneumatic devices.

The availability of brushless DC motors, a better understanding of control mechanisms, in part, through studies of pneumatically powered artificial hearts in animals, and stable miniature sensors have resulted in an

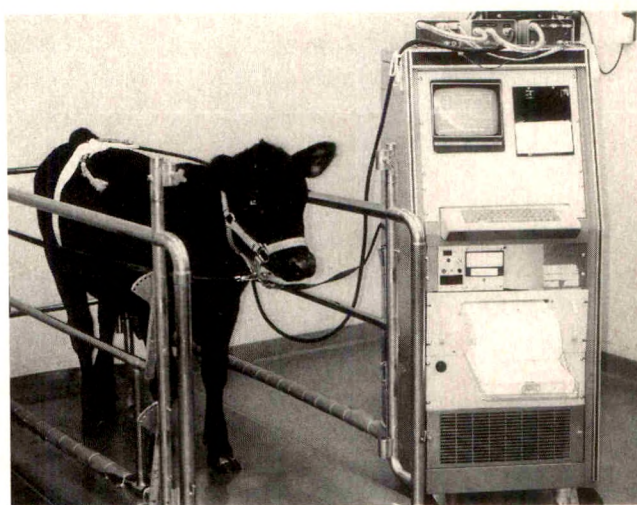


FIG. 3. This calf underwent heart replacement with the roller screw artificial heart. The animal has grown normally and has a good appetite. This photograph was taken 5 months after operation. Hard-wire electric energy transmission is used. The controller has not required adjustment since the first postoperative day. The pressure in the compliance chamber is measured through the subcutaneous access port at 10-day intervals; approximately 30 mL of SF₆ gas is added at that time.

electric heart with the potential for excellent longevity but with no risk of developing dangerously low inlet pressures.

Requirements of minimum size and weight have led investigators to evaluate a variety of interesting techniques to convert rotary motor motion to activate a blood pump sac. A Scotch yoke crank, rack and gear, and a unique double-acting cam have been considered, in addition to the drum cam and roller screw described herein.¹⁴⁻¹⁶ Nasar's group¹⁷ has developed a permanent magnet linear oscillating motor for use in an implantable heart.

For more than a decade, investigators at the University of Utah have pursued the development of an electrohydraulic heart.¹⁸ In their design the energy converter is positioned between two blood pumps similar in design to the Jarvik 7 artificial heart. The energy converter is a motor-driven miniature high-speed reversing axial-flow pump that pumps a volume of silicone fluid, alternately activating one ventricle and then the other. High suction pressures are prevented by the use of a highly stable piezoelectric transducer that senses the fluid pressure behind each ventricle and alters the heart rate accordingly. Each ventricle has a stroke volume of 100 mL and the maximum output is 10 L per minute. The longest period of circulatory support using this device in the calf has been 1 month. Problems with the device center around the motor bearings and the ability to achieve right-left balance.

The animal studies using the heart described herein have used a hard wired system rather than the wireless inductive coupling technique designed for clinical use. This has permitted us to focus on certain elements of the system and to identify problems that had not been identified during bench studies. The flexion life of the elastomeric sac and the maintenance of roller-screw lubrication are of concern but do not represent limiting factors. However moisture diffusion across the blood sacs has resulted in failure of the electrical components. We now encapsulate the electric circuit that contains the Hall effect rotor position transducers with a moisture-resistant aliphatic amine-based epoxy elastomer. To eliminate moisture diffusions other researchers have used a low water permeability butyl rubber overcoat of polymeric materials to exclude moisture from electric components. This approach appears to have worked well.

The major developmental step that remains in our electric heart program is the use of the wireless energy transmission system and implanted electronics in animals. We have obtained a highly sophisticated miniaturized version of our circuit that will allow us to proceed with the implantation of the control circuitry and the NiCd implantable batteries. These components will permit the use and evaluation of the transcutaneous energy transmission system in the experimental animal. A data transmission scheme, similar to that used with pacemakers,

will be used for the bidirectional transfer of data and will be done using a small personal computer attached to the primary coil circuitry. External-to-internal data transfer will be accomplished by frequency-shift keying of the power transmission carrier (± 3 kHz). Directions will be transmitted to the controller during start-up. Controller reprogramming rarely has been required during steady-state operation. However a change in both the baseline cardiac output and aortic pressure cardiac output sensitivity curve may be achieved, if indicated. Internal-to-external data transmission will be based on radio frequency transmission and can be accomplished with the energy transmission system on or off. Available information will include arterial and left atrial pressure, pump parameters, and internal battery voltage.

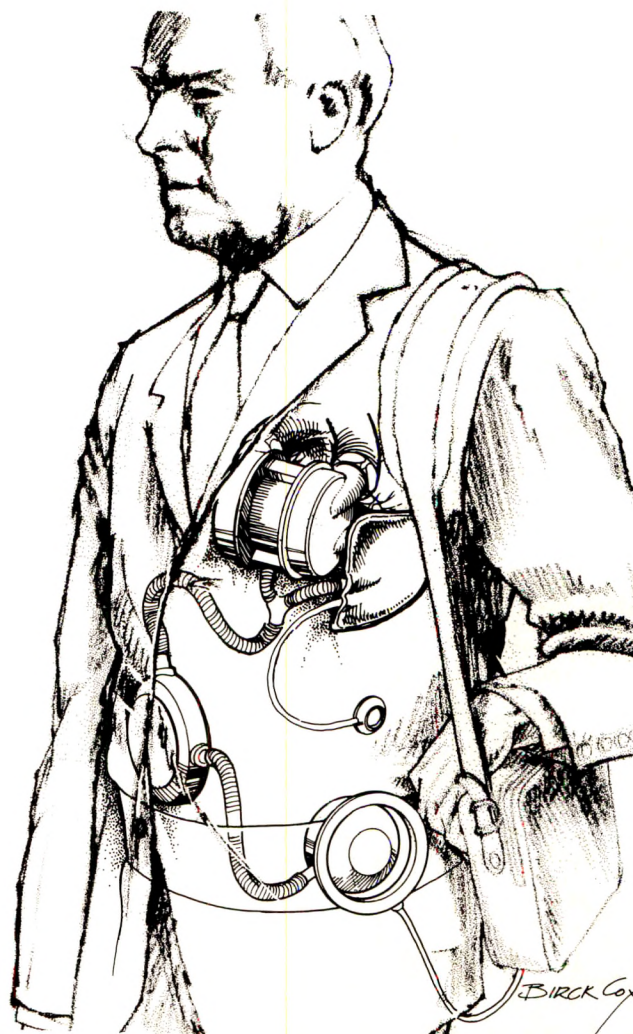


FIG. 4. This sketch shows the proposed application of the electric artificial heart in a human. The electric heart is positioned in the orthotopic location. Other major components include the transcutaneous energy-transfer system (primary and secondary coils), the controller and implantable battery, the compliance chamber positioned in the left pleural space, and the subcutaneous access port.

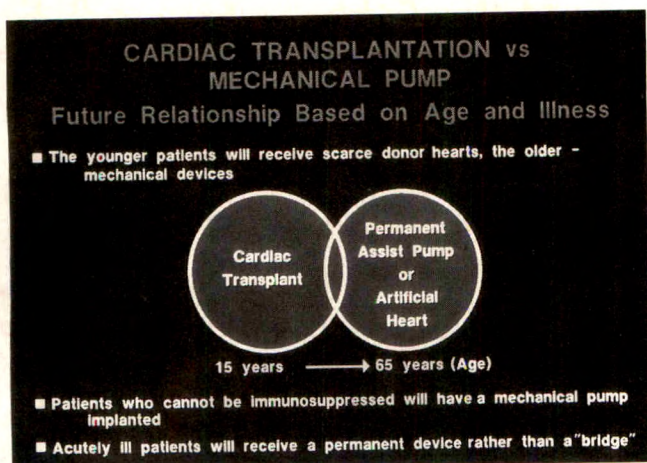


FIG. 5. A close relationship will exist between cardiac transplantation and the artificial heart. Younger patients will receive the less-encumbering transplant, while older patients will receive the artificial heart. Many patients who need but do not receive a transplant in our present system, because of ineligibility or donor shortage, will benefit from the mechanical device.

We believe that the electric heart will ultimately assume an important role, along with cardiac transplantation, in the treatment of end-stage heart disease (Fig. 4). A serious shortage of donor organs exists and may become more critical. Donor organs may be reserved for younger patients while the artificial hearts will be used in older patients. Furthermore the complexities of 'bridging' with the use of a temporary mechanical device followed by transplantation can be overcome by using a permanent device for the original operation (Fig. 5).

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DISCUSSION

DR. HENRY T. BAHNSON (Pittsburgh, Pennsylvania): One has to applaud the perseverance in the face of so many unanswered problems with this project. It is not far fetched to compare this with the days of development of total cardiopulmonary bypass by Gibbon, something that is now used so widely, or even to the development of balloon augmentation, which now can be implanted percutaneously and even done by cardiologists.

In the early days of cardiac surgery every one recognized that total cardiopulmonary bypass was the ideal, but most of us chickened out and used various methods, circulatory arrest with or without hypothermia, the right heart bypass, à la Dewey Dodrill, or the azygous flow principle that was introduced by the Minneapolis group.

I admit we have chickened out also at Pittsburgh, and I speak for my younger associates under the leadership of Dr. Hardesty and Dr. Griffith

who are either home minding the store or presenting papers at the conflicting meeting of the Heart Transplantation Society.

They used the Jarvik, the totally artificial heart, which was the one on your left-hand side in Dr. Pierce's first illustration.

This has been used in 19 patients since 1985, only one of them in the last year. Eight of these 19 patients were long-term survivors after transplantation of the heart. This has been our planned use of the total artificial heart, as a bridge to transplantation.

In all of these patients infection was a problem, and that was the major cause of death in the group, prompting Dick Simmons to remind us that the best antibiotic is a good blood supply.

In contrast to these infection-ridden results with the Jarvik total artificial heart, they have used the Novacor, left ventricular only assist device, in 17 patients. Thirteen of these were subsequently transplanted. All are alive, and infection has not been a major problem.

The longest tenure on this machine, (the left ventricular assist device,)

was 165 days. Encouragingly, although the left heart only was bypassed, the right ventricle improved in its function with the left ventricular assist, and the ejection fraction rose from an average of 13% to 37%.

Infection seemed to be a minor problem in this group of patients, and I wonder what the experience has been in Hershey. Dr. Pierce didn't comment on it, but in the manuscript he mentioned very little concern with infection.

It may be that this ventricular assist device, which is implanted in the subcutaneous tissue with good circulation around it, is less subject to infection than something that is placed into the pericardial sac.

You may know that the Director of the National Heart-Lung Blood Institute, under pressure of a tightening budget, had canceled four contracts for the total artificial heart. He had to restore them under Senatorial pressure but now has instituted another peer review to determine whether they should proceed. I hope the answer to this question will be yes, do proceed.

I encourage Dr. Pierce and his group to continue in their work, and although we have chickened out, I heartily encourage him to hang in there.

DR. MICHAEL E. DEBAKEY (Houston, Texas): As Dr. Pierce indicated, this has been a problem that has concerned researchers for more than 30 years now, but in recent years there is some reason, I think, to be optimistic about the possibility of a fully implantable artificial heart.

My own feeling is that the left ventricular assist device (LVAD) will be more useful than a total artificial heart for application in the immediate future. For example, we believe that the procedure and the mechanism for the LVAD are a little simpler than for the total artificial heart device, and of course, require less wattage. In fact, we have estimated that one can get by with perhaps 4 or 5 W for an LVAD that can provide at least 3000 cc per minute additional output.

A large number of patients fall into that category—much larger than those who might need a total artificial heart. And these are obviously patients who are not going to be candidates for transplantation. If one can increase the cardiac output by another 3000 cc, one can convert many of these patients from being virtually bedridden to at least being ambulatory and able to take care of themselves. For these reasons, I think that the LVAD may have greater potential usefulness in the immediate future.

And thus I would like to ask Dr. Pierce to comment on the work that he has done here on converting this into an LVAD and whether he believes that it has greater immediate usefulness and practicability with regard to experimental work that could lead to the final development.

DR. WILLIAM S. PIERCE (Closing discussion): Dr. Bahnson asked about infection. We have had experience using the total artificial heart and ventricular assist devices in patients as a bridge for cardiac transplantation. We have also noticed that infection has been more of a problem in the total heart than in the left ventricular or biventricular assist application. Accordingly, we favor use of the assist pump for bridging.

There is a difference when we do these operations in animals. We do them at 8 o'clock in the morning. The team is fresh and the animals are healthy; infection rarely occurs. When we do these procedures clinically, it is often a team that has been operating all day, and the patient is ill and there are a lot of other things going on. I attribute at least some of the infection problem to the fact that these are not scheduled cases that are done in a standard fashion. We have really not had a problem in the animal laboratory with infection with any of these devices.

Regarding Dr. Debakey's comments about the left ventricular assistance *versus* the artificial heart, I certainly agree that the first device that is going to come to clinical application is the simpler of the two devices, and that is clearly the permanent left ventricular assist device. We are developing a long-term ventricular device that has many of the same features as this artificial heart, except it does not have the second ventricle. The same motion translator and roller screw are used and seem to work quite well.

Regarding the comment about the power requirements, interestingly, most of the power for pumping the right ventricle seems to be 'free.' The power requirements for the total artificial heart are nearly identical to that of the ventricular assist pump. The pulmonary artery pressures in these normal animals is quite low. The mechanical energy that is used simply in turning the roller screw is similar in the two devices. As a result, there is no difference in the energy consumption in the two devices.

Another comment that Dr. Debakey alluded to was the problem of being able to provide an additional 3 L of flow to a patient's systemic circulation. We certainly agree with that and believe that the original guidelines that had been set by the National Institutes of Health, particularly for assist devices, were excessive. We have downscaled our devices with the belief that being able to pump 3 or 4 L may be adequate.

Skeletal Muscle Ventricles for Total Heart Replacement

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Skeletal muscle ventricles (SMV) were constructed from canine left latissimus dorsi muscle. The animals were divided into three groups: group A (n = 5), SMVs rested 4 weeks without electrical conditioning; group B (n = 6), SMVs rested 4 weeks and then electrically conditioned for 6 weeks; group C (n = 5), SMVs rested 18 weeks without electrical conditioning. At the end of each protocol, the SMVs were acutely tested by connecting them to a mock-circulation device. The SMVs in group C developed stroke work at physiologic preloads superior to any previously reported, as high as 194% of left ventricular stroke work at afterloads of 80 mmHg. The SMVs in group B developed work outputs equivalent to 53% of the left ventricle, which is still more than four times that of the right ventricle. The results show that it is possible to harvest sufficient work from skeletal muscle ventricles to fully replace cardiac function at physiologic preloads.

END-STAGE CARDIAC failure affects a large segment of the world's population.^{1,2} Cardiac transplantation has provided the best treatment, yet donor organs are available to relatively few patients.³ The artificial heart program continues to progress at a slow pace, with thromboembolism and infection as the major stumbling blocks.⁴

The possibility of using an autogenous biologic pump as a cardiac assist device was first raised in 1959,⁵ although the use of skeletal muscle for cardiac reinforcements was described much earlier.^{6,7} Later it was discovered that the normal susceptibility of skeletal muscle to fatigue can be overcome.⁸⁻¹³ Unfortunately it was still difficult to harvest sufficient energy from a skeletal muscle to assist a significantly depressed heart at physiologic preloads. Our goal in this study was to maximize the ability of a skeletal muscle ventricle to do the work needed to sustain the circulation.

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Methods

Skeletal muscle ventricles (SMV) were constructed from the left latissimus dorsi muscle in 16 mongrel dogs (mean weight, 19.2 ± 0.7 kg). The animals were operated on in accordance with the *Guide for the Care and Use of Laboratory Animals* prepared by the National Academy of Sciences.¹⁴ Anesthesia was induced by intravenous thiamylal (12 to 18 mg/kg). The animals were intubated, placed on a ventilator, and maintained on isoflurane (1% to 2%). Prophylactic antibiotics were used, with intravenous cefazolin administered (1 g) before operation, and cephalexin (60 mg/kg/day) given after operation for 14 days.

The left latissimus dorsi was dissected free from the chest, with ligation of all chest wall collaterals. Care was taken to avoid injury to the main neurovascular pedicle. A modified Medtronic electrode (model 6901; Medtronic Inc., Minneapolis, MN) was placed around the thoracodorsal nerve, as described in previous studies.^{9,15,16} The muscle was wrapped, in a spiral fashion, around a Teflon mandrel (manufactured according to our specifications by Biomedical Instrumentation Group, University of Pennsylvania, Philadelphia, PA). The mandrel had a diameter of 3 cm at its base, tapered to a diameter of 2.75, and ended in a hemispherical apex; the mean length was 11.5 ± 0.22 cm, and the total mandrel volume was 70.8 ± 1.0 cc. The SMV was left subcutaneous and the wound closed in layers.

The dogs were entered into one of three protocols. In group A (n = 5) no electric conditioning was applied and the SMV was tested 4 weeks later. In group B (n = 6) the nerve electrode was immediately connected to a fully implantable Medtronic nerve stimulator (model 7421) that was placed under the rectus abdominis. The nerve stimulator was turned on after a 4-week delay. These SMVs were then electrically conditioned for 6 weeks at a continuous frequency of 2 Hz, using pulses of 210 μ sec duration, at an amplitude of three times threshold (0.75 to 1.5 volts). In group C (n = 5) the SMVs were rested for

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TABLE 1. Comparison of the Experimental Groups

Group	n	Dog Weight (kg)	Mandrel Size (mL)	Delay (weeks)	Conditioning (weeks)
A	5	20.2 ± 0.8	73.0	4	0
B	6	18.0 ± 1.1	70.0 ± 1.9	4	6
C	5	19.5 ± 1.7	69.4 ± 2.2	18	0

Values are mean ± SEM.

18 weeks without electrical conditioning. Table 1 summarizes the data for the three groups.

Measurements

At the completion of each specified protocol, the animal was anesthetized and, after removal of the Teflon mandrel, the SMV was connected to a mock-circulation device. The mock-circulation device was described before,^{10,15,17,18} and its features are illustrated in Figure 1. The mock circulation allows for control of both preload and afterload. A typical pressure tracing obtained from one of the dogs in group C is shown in Figure 2. An analytical solution for the mock-circulation device is used to calculate stroke work (SW):¹⁶

$$SW = P_1 V_1 [\ln(V_1) - \ln((P_1/P_2)V_1)] - P_3 V_1 ((1 - (P_1/P_2))$$

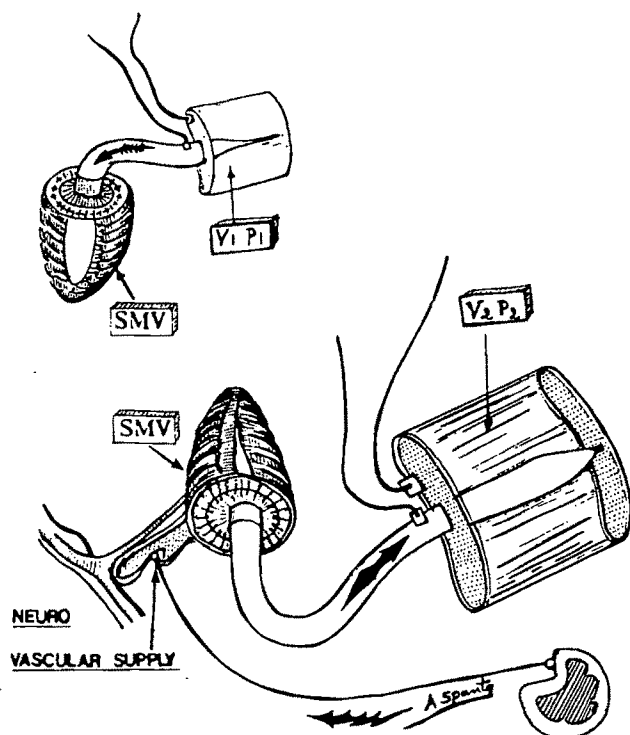


FIG. 1. Skeletal muscle ventricles (SMV) connected to the mock circulation device. SMV end diastole and end systole are diagrammed. The pressure of the cannister is the afterload. The pressure of the saline column is the preload. Given the closed system, Boyle's Laws applies: $V_1 P_1 = V_2 P_2$.

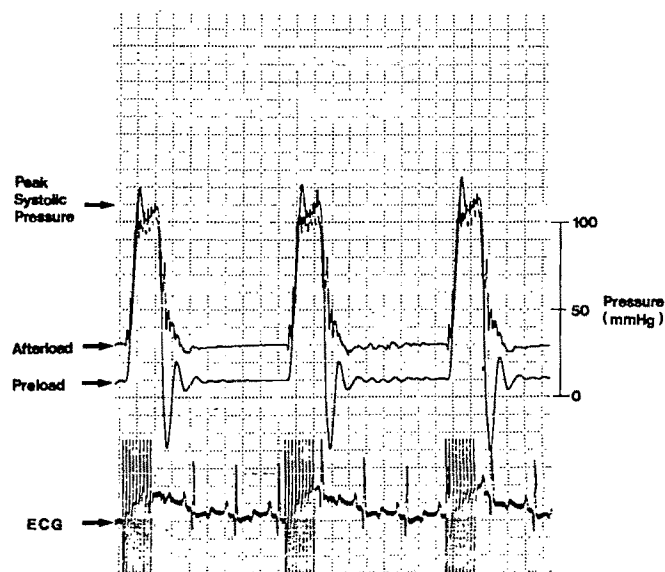


FIG. 2. Typical pressure recording from a dog in group C. Stimulation frequency = 25 Hz, afterload = 30 mmHg, preload = 10 mmHg, SMV systolic pressure = 112 mmHg.

where P_1 = afterload, P_2 = SMV systolic pressure, P_3 = preload, and V_1 = cannister volume.

All thoracodorsal nerve electrodes were connected to a Medtronic 7421 nerve stimulator set at the following parameter: duty cycle = 310 msec on, 1.5 sec off; amplitude = 4 volts (supramaximal); pulse width = 210 μ sec. All measurements were taken first with the burst frequency set at 25 Hz and then repeated at 85 Hz.

For all groups the afterload was set first at 30 mmHg, and recordings were taken while the preload was increased gradually from near 0 to 20 mmHg. The afterload was then set at 80 mmHg and data were obtained as the preload was increased from 0 to 50 mmHg. An endurance test was carried out on eight of the dogs for 1 hour at the preload of 20 mmHg and the afterload of 30 mmHg.

Histology

Samples were removed for histologic assessment from proximal (basal), middle, and distal (apical) portions of the SMVs. The tissue was fixed in formalin and embedded in paraffin. Sections were cut at 5- μ m thickness and stained with hematoxylin and eosin for light microscopic examination.

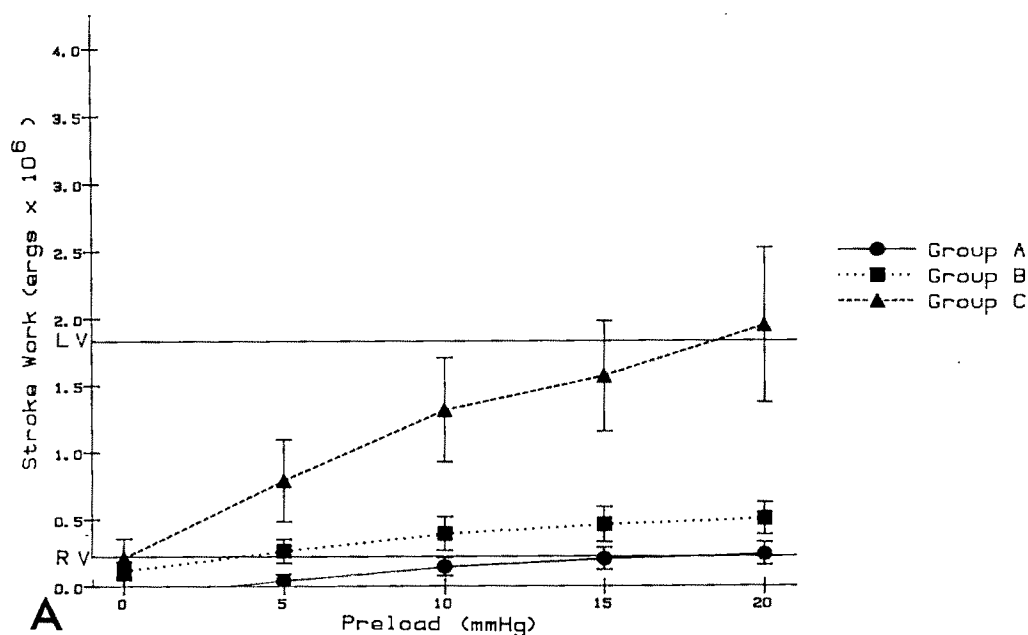
Statistics

Comparison of the groups by a one-way analysis of variance was carried out using an RS/1 statistical software package (Copyright 1986, Bolt Beranek and Newman, Inc., Cambridge, MA) on a Toshiba portable computer (Toshiba America Inc., Irvine, CA).

Results

The performance of the groups at the stimulation frequency of 25 Hz is summarized graphically in Figures 3A

FIG. 3. Stroke work is plotted versus preload for all three groups. Left ventricular (LV) stroke work and right ventricular (RV) stroke work, previously calculated from weight-matched dogs, are superimposed for comparison (RV sw = $0.22 \pm 0.11 \times 10^6$ ergs, LV sw = $1.83 \pm 0.98 \times 10^6$ ergs)¹⁸ (A) Frequency = 25 Hz, afterload = 30 mmHg.

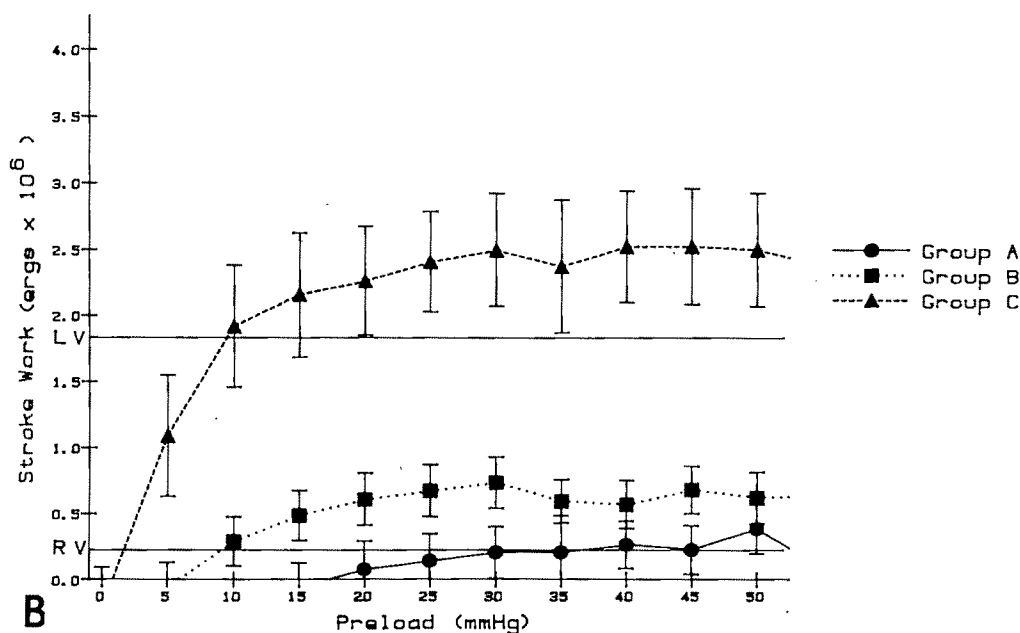


and B. Values for weight-matched canine left ventricular (LV) and right ventricular (RV) stroke work from a previous determination¹⁹ are also charted. At preloads of more than 5 mmHg and an afterload of 30 mmHg, SMVs from groups B and C generated stroke work greater than that of the canine RV, with SMVs from group C generating 356% of RV stroke work at a filling pressure of 5 mmHg. At a preload of 10 mmHg, similar to left ventricular end diastolic pressure, and an afterload of 80 mmHg, SMVs from group C developed stroke work 105% that of the LV. Comparison of the three groups by one-way analysis of variance shows statistically significant dif-

ferences at filling pressures greater than 0 mmHg (for afterload = 30 mmHg: $p \leq 0.03$ at preload = 5, $p < 0.006$ at preload = 10, $p < 0.003$ at preload = 15, $p < 0.004$ at preload = 20; for afterload = 80 mmHg: $p < 0.02$ at preload = 5, $p < 0.001$ at preloads = 10 to 50).

The performance of the groups at the stimulation frequency of 85 Hz is graphed in Figures 3C and D. At preloads of more than 5 mmHg and an afterload of 30 mmHg, all three groups exceeded RV stroke work, with SMVs in group C surpassing LV stroke work at a preload of 10 mmHg. At a preload of 10 mmHg and an afterload of 80 mmHg, mean SMV stroke work from group C

FIG. 3B. Frequency = 25 Hz, afterload = 80 mmHg.



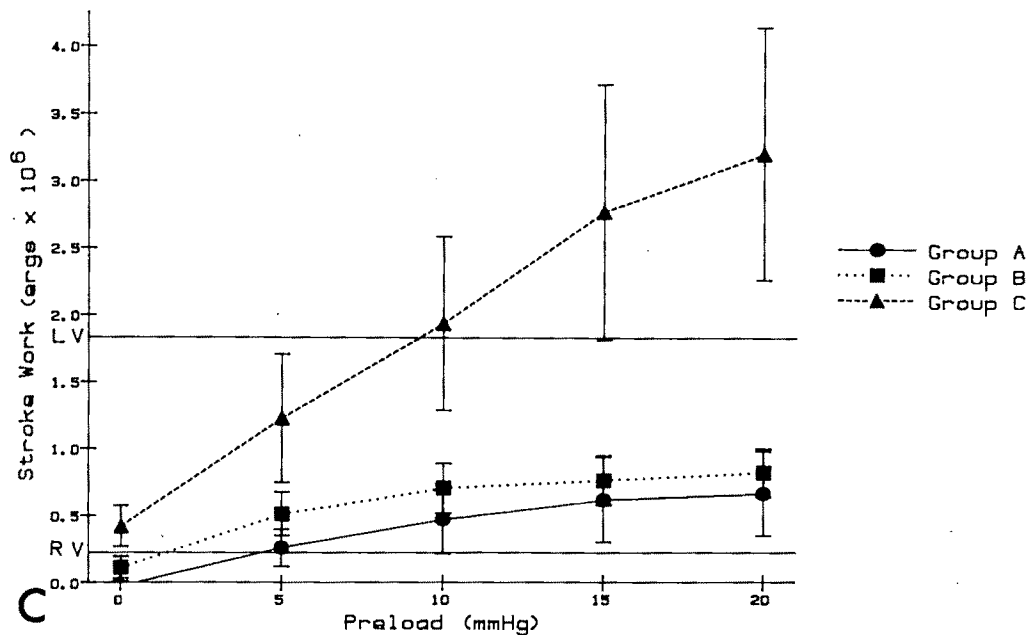


FIG. 3C. Frequency = 85 Hz, afterload = 30 mmHg.

reached 142% of LV stroke work. At a preload of 25 mmHg and an afterload of 80 mmHg, group C reached a maximum level at 194% of LV stroke work. Comparison of the three groups by a one-way analysis of variance shows statistically significant differences at all preloads (afterload = 30 mmHg: $p < 0.03$ at preload = 0, $p < 0.08$ at preload = 5 mmHg, $p < 0.04$ at preload = 10 mmHg, $p < 0.02$ at preload = 15, $p < 0.007$ at preload = 20; for afterload = 80 mmHg: $p < 0.02$ at preload = 0, $p < 0.004$ at preload = 5, $p < 0.001$ at preloads = 10 to 50).

The results of the eight SMVs that underwent endurance testing are shown in Figure 4 (group A, $n = 4$; group B, $n = 3$; and group C, $n = 1$). The electrically conditioned

SMVs (group B) perform at 83% of baseline at 60 minutes, while the SMVs in group A (4-week delay, unconditioned) perform at 52% of baseline at 60 minutes. The single SMV tested in group C performs more like conditioned SMVs than like unconditioned SMVs, with 70% of power output at 60 minutes. Even at 60 minutes, when stroke work decreased by 30%, the mean stroke work of group C was 271% that of group B (conditioned).

Histology

The inner surface of the SMVs consisted of a continuous, smooth, compact fibrocellular layer, supported by

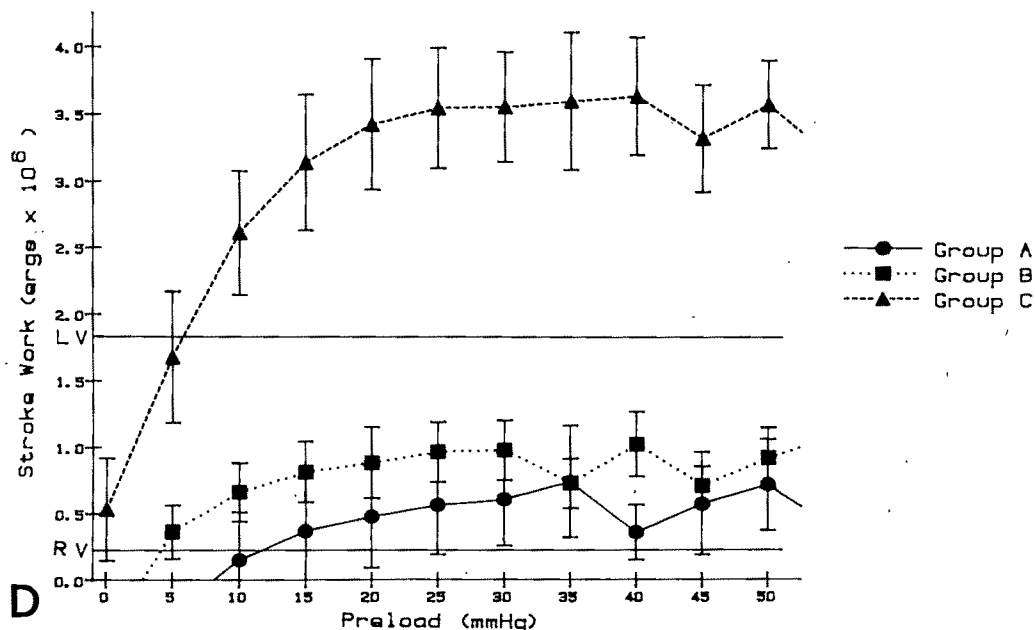
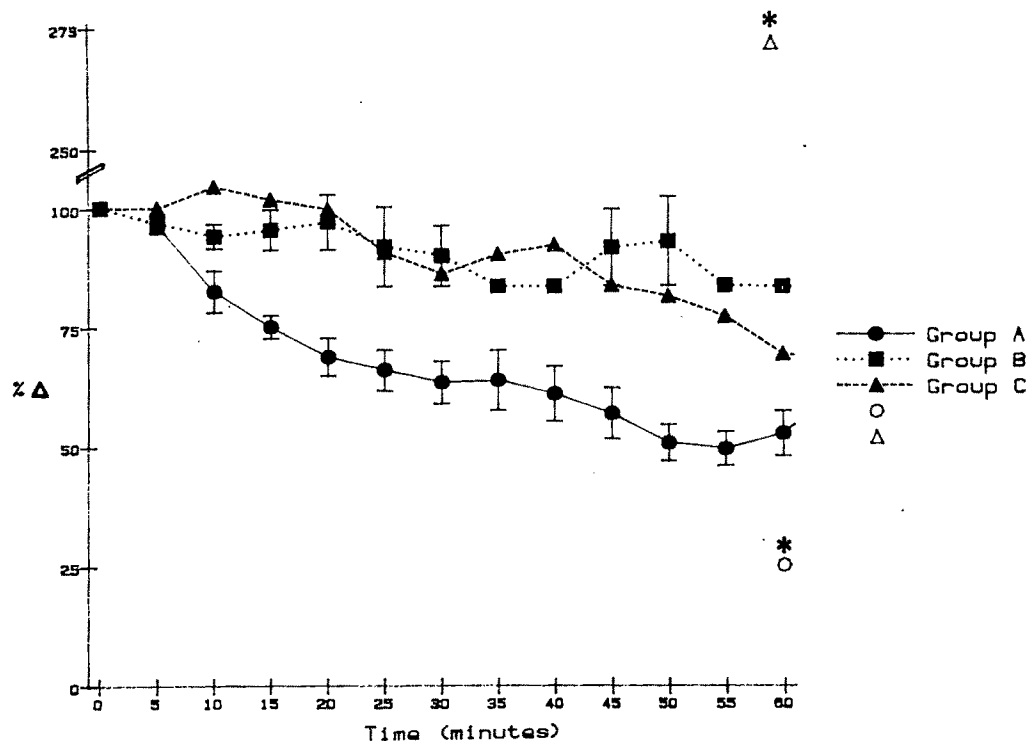


FIG. 3D. Frequency = 85 Hz, afterload = 80 mmHg.

FIG. 4. Endurance test. Percentage change in stroke work for each group *versus* time. The empty symbols highlighted by * compare the stroke work of groups A and C to group B at 60 minutes. Mean SMV sw in group C at 60 minutes is 271% that of group B. Mean SMV sw in group A at 60 minutes is 25% of group B.



a thicker layer of fat and loose connective tissue. The outer surface was less organized. In some samples there was a more deeply placed layer of adipose or fibrous connective tissue, which may have corresponded to the interface between successive wraps of the muscle. In such layers there was evidence of muscle degeneration with connective tissue replacement. Foreign-body giant cell and macrophages were found, usually in relation to suture debris. In about one half of the SMVs, the muscle tissue adjacent to these layers was not grossly abnormal, although it showed a tendency to excessive nuclearity, some thickening of perimysial septa, intrafascicular fat cells, and some internal nuclei. In the remaining SMVs the muscle underwent more extensive cellular infiltration and necrotic changes in at least one of the portions sampled, although not necessarily in all. The tissue appeared to be well vascularized, but the larger blood vessels had thickened walls. Many sections contained nerves, which appeared normal. Muscle from the 4-week, unconditioned group A differed only in showing more acute signs of infiltration and muscle degeneration. Muscle from the conditioned group B had smaller fibers of rounded profile, which contained abundant nuclei and were separated by more extracellular space than normal; such appearance is typical of chronically stimulated muscle.^{20,21}

Discussion

Skeletal muscle has two to four times the power of cardiac muscle per gram of tissue.²² The latissimus dorsi

muscle has approximately the same mass as the left ventricle in both humans and dogs.¹⁶ Therefore it should be possible to generate the power necessary to sustain the circulation from a single latissimus dorsi muscle. A number of factors have prevented this ideal from being achieved.

The first difficulty was fatigue; in the early experiments striated muscle lost nearly all of its power within a few minutes.^{5,23,24} Later studies on cross-innervation of skeletal muscle and on direct chronic nerve stimulation showed that a fast-twitch, fatigue-prone muscle could be changed into a slow-twitch, fatigue-resistant muscle.^{8-13,25,26} Such knowledge opened the way to the use of skeletal muscle for cardiac assist.

A second problem was compliance. In 1974 Spotnitz²³ constructed skeletal muscle pouches from the canine rectus muscle. He found the geometric and physical characteristics similar to those of the heart described by Frank and Starling. This observation should not have been surprising because Otto Frank, in 1895, recognized that the response of isolated frog heart to alteration in tension just before contraction was similar to that of skeletal muscle.²⁷ With filling pressures of 50 to 150 mmHg, Spotnitz obtained systolic pressures of more than 500 mmHg. However, with such noncompliant skeletal muscle pouches, it is unlikely that they could have been used for cardiac assist, even if they had not fatigued rapidly. This problem of low skeletal muscle compliance raised by Spotnitz represented a potential difficulty in using skeletal muscle for cardiac assist. However, with the use of the latissimus

dorsi muscle and with appropriate design and construction, compliance has not been a significant problem in our laboratory.^{17,18,28}

Some groups have put their efforts into wrapping a pedicle muscle graft around a great vessel or the heart itself (cardiomyoplasty).²⁹⁻³⁵ These approaches are appealing for their simplicity and for the fact that no muscle or artificial material comes into direct contact with blood, thus avoiding thromboembolic complications. However Laplace's Law predicts that the latissimus dorsi muscle wrapped around the heart could generate only moderate work, thus failing to use the full potential of skeletal muscle.

Other researchers have focused on the design and use of SMVs constructed from canine latissimus dorsi muscle.^{10,15,17,18, 23,24,36-42} Until now we too had been unable to harvest the work output potential of skeletal muscle.^{17,18} The best-performing SMVs could generate only up to 70% of LV stroke work at a preload of 30 mmHg, an afterload of 80 mmHg, and a stimulation frequency of 85 Hz.¹⁷

The present study demonstrates, for the first time, that an SMV can generate a power output exceeding that of the left ventricle, and approaching its full potential. At filling pressures similar to those encountered by the LV (10 mmHg) and at an afterload of 80 mmHg, an SMV generated 105% of LV stroke work at a frequency of 25 Hz and 142% of LV stroke work at a frequency of 85 Hz. In Figure 5 the present results are compared to the two best groups (groups III and IV) from a previous study.¹⁷ The marked improvement in the performance of group C is easy to detect.

This acute study raises the question as to whether this performance could be sustained. We tried to answer this

question in a preliminary way by performing a 60-minute endurance test. Although 30% of power output from the dog in group C was lost at 1 hour, the remaining stroke work is still 271% better than our next-best result from group B. Our previous studies on conditioning patterns showed that most of the loss of working capacity in unconditioned skeletal muscle occurred during the first 30 minutes, and that there was at least a partial recovery by 48 to 72 hours.¹⁴ Although more specific studies must be done, previous work with SMVs^{15,37,40,42} indicates that a significant portion of the SMV power output could be maintained chronically.

Earlier research established that chronic electric stimulation at a continuous frequency of 2 Hz for a period of 6 weeks substantially improved skeletal muscle fatigue resistance.¹⁶ The improved fatigue resistance was accompanied by a reduction in work output.^{13,16,43} In the present study the SMVs in the conditioned group B performed approximately as well as the SMVs from the best unconditioned groups previously reported and considerably better than the SMVs in the unconditioned group A. The present study suggests that conditioning is not the only factor responsible for the decreased work output accompanying electric conditioning.

The most important question regarding this study is how the improvement in SMV function was achieved. The mandrel size, which was larger than in some previous studies, probably did not play a crucial role because the other two groups in this study, with SMVs constructed around the same size mandrel, behaved as in our previous experience. The longer delay (18 weeks) after construction of the SMV probably contributed most to the improved outcome. It is our experience that at the time of SMV

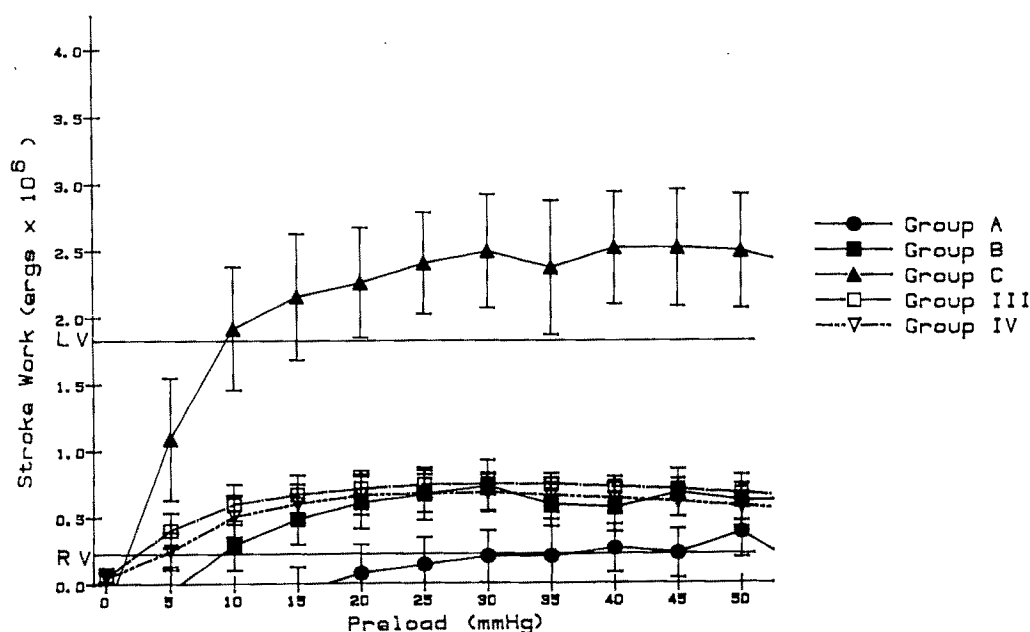


FIG. 5. Stroke work versus preload at 25 Hz, and afterload = 80 mmHg. Superimposed on the three groups from this study are the best groups (III and IV) from a previous study carried out in this laboratory.¹⁷

construction the distal one third to one half of the canine latissimus dorsi is severely ischemic.^{19,44} The muscle may take longer than we had suspected to recover sufficient vascular supply to function effectively. It is also possible that during the 18-week delay some adjustment occurred in the internal architecture and length of the muscle fibers, resulting in a more effective adaptation to the new geometry.

The histologic appearance of the samples showed little or no relationship to the actual performance of the SMVs from which they were derived. This was probably due, in large part, to the difficulty of obtaining adequately representative samples from a structure that is complex, deformable, and inhomogeneous. It also reflects the observation, common among those who study muscle composition in normal individuals and athletes, that severe histopathologic changes sometimes can be seen in biopsy samples from muscles that had been functioning in an apparently satisfactory and symptom-free manner. The histologic findings clearly indicate, however, that there is scope for further development of surgical techniques for the construction of SMVs that will assure the survival of a larger proportion of the original muscle.

Can such SMVs perform as well in the circulation? In another study we have shown that a SMV can pump blood effectively as an aortic diastolic counterpulsator for at least 9 months.⁴⁰ In that dog model no thromboembolic events were observed.

The present study indicates that it is possible to construct skeletal muscle ventricles that can generate, under acute conditions, more work than the left ventricle at physiologic filling pressures. It must be shown whether this performance could be sustained chronically, although this study raises the possibility that electric conditioning could be achieved without significant power losses. If this power output could be maintained in circulation, there would be a prospect of replacing cardiac function entirely by means of SMVs.

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DISCUSSION

DR. GEORGE J. MAGOVERN (Pittsburgh, Pennsylvania): I rise to congratulate Dr. Stephenson and his group. They have long been pioneers in the field of skeletal muscle plasticity and particularly in using the latissimus dorsi. We have similarly been involved, although not in exactly the same manner, primarily in wrapping the latissimus around the left ventricle. The common finding is that the longer the muscle is in place, the better the collateral circulation that develops. Some of our measurements indicate that the blood flow for the resting latissimus in canines is about 8 mL/minute and after stimulation it goes up to 80 mL/minute. Therefore, as Henry said earlier, a good blood supply is necessary to maintain the normal metabolic and physiologic functions of the muscle.

This report by Dr. Stephenson is really a dramatic change from his previous work in which he routinely insisted that the latissimus dorsi had to be stretched to almost its normal length and to have, so to speak, a left ventricular end diastolic pressure of 30 mmHg before one could get an effective contraction. Now you have shown us that you can get the same or better contraction with a so-called left ventricular end diastolic pressure of 10 mmHg. I think that this is really a seminal finding, although it is similar to what other people have been saying for some time. I am concerned, however, that you had to get to 85 Hz to generate this type of pressure, and I believe that would probably lead to fibrosis of the muscle over time.

DR. GEORGE F. SHELDON (Chapel Hill, North Carolina): How do you intend to resolve the issue of whether the performance improvement is due to collateral circulation or just to muscle fiber reorientation?

DR. ALBERTO POCHETTINO (Closing discussion): Regarding the stimulation frequency at which these results were obtained: At 25 Hz, which is the frequency used successfully in our chronic studies, the results show that 105% of left ventricular stroke work is achieved at a preload of 10 mmHg. Of course, higher work outputs are obtained at 85 Hz, but at 25 Hz, which is tolerated well chronically, we can achieve adequate stroke work.

Regarding Dr. Sheldon's remark: Is the improved performance due to increased collateral circulation, or to muscle fiber reorientation? We do not as yet have an answer to that question. The reason we raise that issue is because, while our previous studies have shown a significant improvement in vascularization with long delays, we do not think that neovascularization continues to occur after 5 or 6 weeks. It seems that there is something else going on, which could possibly be due to fiber reorientation.

We are aware of the technical difficulties involved in studying this issue; we are, however, working on an experimental design that may address that question.

Renal Transplantation in Infants

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The timing of renal transplantation in infants is controversial. Between 1965 and 1989, 79 transplants in 75 infants less than 2 years old were performed: 23 who were 12 months or younger, 52 who were older than 12 months; 63 donors were living related, 1 was living unrelated, and 15 were cadaver donors; 75 were primary transplants and 4 were retransplants. Infants were considered for transplantation when they were on, or about to begin, dialysis. All had intra-abdominal transplants with arterial anastomosis to the distal aorta. Sixty-four per cent are alive with functioning grafts. The most frequent etiologies of renal failure were hypoplasia (32%) and obstructive uropathy (20%); oxalosis was the etiology in 11%. Since 1983 patient survival has been 95% and 91% at 1 and 5 years; graft survival has been 86% and 73% at 1 and 5 years. For cyclosporine immunosuppressed patients, patient survival is 100% at 1 and 5 years; graft survival is 96% and 82% at 1 and 5 years. There was no difference in outcome between infants who were 12 months or younger *versus* those who were aged 12 to 24 months; similarly there was no difference between infants and older children. Sixteen (21%) patients died: 5 after operation from coagulopathy (1) and infection (4); and 11 late from postsplenectomy sepsis (4), recurrent oxalosis (3), infection (2), and other causes (2). Routine splenectomy is no longer done. There has not been a death from infection in patients transplanted since 1983. Rejection was the most common cause of graft loss (in 15 patients); other causes included death (with function) (7), recurrent oxalosis (3), and technical complications (3). Overall 52% of patients have not had a rejection episode; mean creatinine level in patients with functioning grafts is 0.8 ± 0.2 mg/dL. Common postoperative problems include fever, atelectasis, and ileus. At the time of their transplants, the infants were small for age; but with a successful transplant, their growth, head circumference, and development have improved. Transplantation in infants requires an intensive multidisciplinary approach but yields excellent short- and long-term survival rates that are no different from those seen in older children or adults. Living donors should be used whenever possible. Patients with a successful transplantation experience improved growth and development, with excellent rehabilitation.

THE FIRST SUCCESSFUL kidney transplants were performed less than 40 years ago. Shortly thereafter Riley¹ raised ethical concerns about renal transplantation in children and suggested that two factors, 'length of prolongation of life' and 'discomfort,' must be

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balanced. In 1970 Reinhart² seriously questioned 'the value of chronic dialysis or renal transplant' for children with end-stage renal disease (ESRD). Since then rapid progress had been made, and by 1980 hemodialysis and renal transplantation were accepted treatments for older children and adolescents.³ However the value of such treatment for the young child or infant with renal failure remained in question. As recently as 1988, Fine stated, 'It is difficult to advocate renal transplantation in infants and young children with ESRD as the preferred treatment.'⁴

We believe the best chance an infant with ESRD has for achieving normal development and a normal lifestyle is a successful transplant. To that end we strongly recommend living related donor transplants for infants and small children; for those without a living donor, we think a cadaver transplant is preferable to chronic dialysis or withdrawal of support. In this paper we review the results of transplantation in 75 infants who were less than 2 years old. With current immunosuppressive protocols, patient and graft survival rates are no different in these smaller and younger patients than in older children and adults.

Material and Methods

Recipients

Between January 1, 1965 and December 31, 1989, 75 infants less than 2 years old (6 weeks to 24 months) received 79 kidney transplants at the University of Minnesota (Fig. 1). Of these patients 63 had living related donors (LRD); 15 received cadaver organs; and 1 had a living unrelated donor. The etiology of renal failure is listed in Table 1; hypoplasia and obstructive uropathy accounted for 52% of the patients. Infants with kidney disease are initially evaluated by a multidisciplinary team, including pediatric nephrologists, surgeons, neurologists, nutritionists, clinical psychologists, and social workers. Ideally evaluation occurs before dialysis is instituted, thus allowing time to define the disease etiology, explore treatment options, and evaluate potential donors. The rela-

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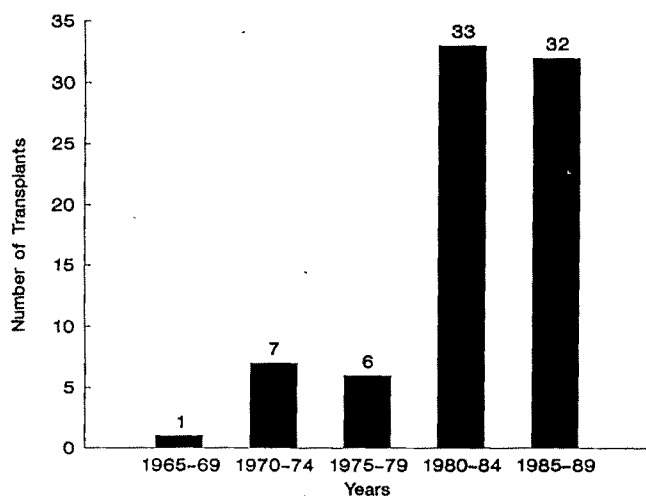


FIG. 1. Number of transplants in infants during 5-year intervals (1965 to 1989).

tively few contraindications to transplantation include active infection, malignancy, or serious irreversible brain injury. If parents of children with severe developmental delay prefer transplantation, after being carefully informed that dramatic improvement in neurologic function is unlikely, the transplant is performed.

The recipient workup includes structural evaluation of the native kidneys as well as a voiding cystourethrogram (VCUG) to evaluate bladder function and reflux. Renal biopsy may be needed for diagnosis in some patients. Patients with ureteral reflux or polycystic kidneys need bilateral ureteronephrectomy at the time of the transplant. Significant nephrotic syndrome also requires bilateral nephrectomy and at least 6 weeks of dialysis support to correct nutritional defects before the transplant surgery.⁵ After appropriate surgical treatment, patients with extrarenal congenital anomalies have been accepted for transplantation. Children with primary oxalosis are evaluated and managed as previously described.^{6,7}

Donors

The child's family is encouraged to identify potential LRDs. While the recipient workup is in progress, potential donors are screened and HLA typing is determined. Initial criteria for consideration include ABO compatibility, a negative crossmatch, and no history of disease that might affect the kidneys (e.g., hypertension, diabetes). Further donor workup includes a complete medical history and physical exam, along with laboratory tests to determine that the potential donor is an excellent surgical risk and has two well-functioning kidneys. Once accepted the donor is admitted to the hospital and an arteriogram is performed to define the renal vascular anatomy. Finally, before the transplant, the crossmatch is repeated.

One patient without an LRD received a kidney from a living unrelated donor. The donor workup was as above; in addition the potential donor was interviewed by a psychiatrist to ensure informed consent and altruistic motivation. Patients without a living donor were put on the waiting list for a cadaver donor transplant. Before 1987 an attempt was made to match HLA antigens when cadaver kidneys were used; however a poor match was not considered a contraindication to transplantation. Since 1987 the extant United Network for Organ Sharing (UNOS) point system has been used to allocate cadaver kidneys.

Perioperative Management

The surgical technique and perioperative management have been previously described.⁸⁻¹² Recipients of living donor transplants are admitted to the hospital at least 3 days before transplantation. This time is used to perform presurgical teaching of the family, while metabolism, anemia, infection, blood pressure, and the need for dialysis are all assessed in the recipient.

Perioperative antibiotics (third-generation cephalosporins) are administered on the morning of surgery. The operating room temperature is maintained at 32 C and the recipient is placed on a warming blanket to reduce the risk of hypothermia. In the operating room, after induction of anesthesia, an arterial line is placed to monitor blood pressure; if not already present, a Hickman catheter suitable for hemodialysis is placed. The catheter is used also to measure central venous pressure (CVP), administer medication, and draw blood. A rectal probe is placed to monitor core temperature.

Using warmed solutions the entire abdomen and perineum is prepped and draped into the operative field. A Foley catheter or large infant feeding tube is then placed into the bladder. Prepping the perineum and catheter into the field allows manipulation of the catheter during the operation. All infants are surgically approached through

TABLE 1. Etiology of ESRD in 75 Infants

Etiology	No. of Patients	Percentage
Hypoplasia	24	32
Obstructive uropathy	15	20
Oxalosis	8	11
Congenital nephrotic syndrome	6	8
Hemolytic uremic syndrome	4	5
Cortical necrosis	3	4
Infantile polycystic kidney disease	3	4
Glomerulonephritis	3	4
Steroid resistant nephrotic syndrome	2	3
Birth hypoxia with renal failure	2	3
Jeune's syndrome	1	1
Drash syndrome	1	1
Anatomical problems	1	1
Unknown	2	3

a transabdominal incision. At this point bilateral ureteronephrectomy, if necessary, is done. In all infants the cecum and right colon are mobilized. The aorta is dissected from the inferior mesenteric artery to the external iliac artery on the right. Lumbar branches are ligated and divided; the right external and internal iliac arteries and left common iliac are encircled. The inferior vena cava and common iliac veins are dissected and the lumbar veins ligated. When the donor kidney is ready, the proximal aorta and vena cava and the iliac vessels are occluded; no heparin is given to the recipient. The venous anastomosis is then performed between the donor renal vein and distal vena cava or right iliac vein; an end-to-side arterial anastomosis is then done between the donor renal artery and the distal aorta or common iliac artery.

Before reperfusion of the kidney, the infant's CVP is raised to 15 to 18 cm of water by administering plasmanate and/or packed red blood cells. It is vital during reperfusion to maintain adequate blood pressure and filling pressures *via* volume expansion. Mannitol (250 mg/kg) and furosemide (1 mg/kg) are infused as the anastomoses are completed. Before release of the clamps, the kidney is warmed with saline to counteract the hypothermic effect of the cold perfusate used to flush the kidney. At the same time sodium bicarbonate (1 mEq/kg) is given to neutralize the acidotic blood released from the legs. The kidney is then placed in the right retroperitoneal space. The ureter is implanted into the bladder using a standard Leadbetter-Politano technique. Frequently the ureteral anastomosis is stented with a silastic feeding tube.

Postoperative management includes meticulous attention to fluid and electrolyte replacement status.^{9,10} Intravenous fluids are administered on a milliliter-per-milliliter basis to match urine output. The composition of the solution is frequently readjusted, depending on the results of serum and urinary electrolyte determinations performed at least every 6 hours during the first 2 postoperative days. Colloid is used to maintain adequate intravascular volume and replace third-space loss. The adequacy of replacement therapy is assessed by monitoring pulse rate, blood pressure, peripheral perfusion, arterial blood gases, CVP, and, if necessary, chest x-ray. No one factor alone (*e.g.*, CVP) is used to assess intravascular volume. For example some infants can be volume overloaded with CVPs in the range of 3 to 4 cm H₂O, while others can tolerate much higher CVPs. If hyperglycemia is present, the urine replacement solution is changed to a 1 g/dL glucose base. Calcium levels are carefully followed and calcium is replaced intravenously as needed; there is a significant incidence of hypocalcemia in the early postoperative period. Oliguria associated with an adequate intravascular volume is treated with intravenous furosemide (1 mg/kg).

A prolonged ileus is frequent after operation and nasogastric drainage is required. If, before operation, the

infant is thought to be nutritionally deficient, hyperalimentation is begun early in the postoperative period. If a ureteral stent has been placed, a dye study through the stent is performed on postoperative day 5 and the stent is removed if the study is normal. The Foley catheter is discontinued on postoperative day 7. By this time a regular diet is usually tolerated.

Immunosuppressive Protocols

The immunosuppressive protocols for pediatric recipients at our institution have been previously described.⁸⁻¹² Briefly, between January 1965 and June 1984, standard immunosuppression consisted of azathioprine (5 mg/kg/day tapered to 2.5 mg/kg/day at 1 week), prednisone (2 mg/kg/day tapered to 0.2 to 0.3 mg/kg/day at 1 year), Minnesota antilymphoblast globulin (MALG) (30 mg/kg/day for 14 days), and methylprednisolone (20 mg/kg/day for 3 days). In addition, after 1979, all patients received three to five random donor blood transfusions before transplantation, most recently while receiving 1.5 mg/kg/day of azathioprine. Rejection episodes were documented by biopsy and treated with increased prednisone doses to 2 mg/kg/day. In addition first rejection episodes were commonly treated with MALG (20 mg/kg/day for 7 to 10 days). Before 1984 splenectomy was done before or at the time of the transplant in almost all patients. At that time results of a prospective randomized trial indicated that splenectomy had no long-term benefit on graft function.¹³ Thus routine splenectomy was abandoned.

In June 1984 a protocol evaluating pretransplant donor-specific transfusions (DST) was instituted.¹⁴ Three DSTs were administered before operation, one each at 2-week intervals. Patients were then crossmatched 4 to 6 weeks later to evaluate sensitization; if the crossmatch was negative, we proceeded with transplantation. After operation such patients received MALG, prednisone, and azathioprine. Seven infants entered the DST protocol and underwent transplantation; outcome was identical to other noncyclosporine immunosuppressed patients and the data have been combined.

Since 1984 non-DST infants and cadaver transplant recipients have received sequential therapy: MALG (20 mg/kg for 14 days), prednisone, and azathioprine at the time of the transplant with cyclosporine (CSA) (2.5 mg/kg twice a day) added on postoperative days 10 to 12. Initially infants and children were completely weaned from CSA; currently the CSA dose is reduced at 1 month to 2 mg/kg twice a day and at 2 months to 1.5 mg/kg twice a day. No effort is made to maintain a specified CSA blood level. If rejection is suspected,¹⁵ percutaneous allograft biopsy is done to confirm the diagnosis. Rejection episodes are treated by increasing the steroid dose. Steroid-resistant rejections are treated with an additional 7- to

10-day course of MALG. For patients experiencing rejection, the CSA dose is increased and an attempt is made to maintain whole blood trough levels, as measured by high-performance liquid chromatography (HPLC), between 75 and 125 ng/mL.

After transplantation all patients received daily oral trimethoprim and sulfamethoxazole to prevent *pneumocystis carinii*, *Nocardia*, and *Listeria* infection. Splenectomized patients are also maintained on daily penicillin to reduce the risk of postsplenectomy sepsis. Oral nystatin is always prescribed to minimize the risk of opportunistic fungal overgrowth during the immediate post-transplantation period and during rejection treatments. Infants also receive hepatitis B vaccine and routine childhood immunizations before transplantation. If the normal immunization schedule is interrupted by transplantation, it is resumed about 6 months after transplantation; but live virus vaccines are never used.

Data Analysis

The 75 children were followed for a minimum of 3 months after their primary transplants. Graft and patient survival rates for the first transplant were analyzed according to age at transplantation (≤ 12 months *versus* 12 to 24 months), donor source (LRD) *versus* cadaver donor (CAD), era (before 1983 *versus* after 1983), and immunosuppressive management (non-CSA *versus* CSA). Graft failure was defined as return to dialysis, transplant nephrectomy, retransplant, or death with a functioning graft. All deaths, including those after return to dialysis, are included. The four retransplants are considered separately.

We compared graft and patient survival rates for infants who were less than 2 years old *versus* older children during the same period. In addition, for infants, we analyzed postoperative complications, cause of graft loss, and cause of death. Growth data were obtained by retrospective chart review. The data were then converted to standard deviation scores (SDS) using the formula:

$$\text{SDS} = (\text{Patient value} - \text{Mean value}) / \text{standard deviation}$$

The normal values are those published for American children.¹⁶

The psychometric data was part of a prospective developmental analysis begun in 1980. The youngest children were evaluated before transplantation using the Bayley Scales of Infant Development. The scales have a mean value of 100, with a standard deviation of 16. Older children were tested with age-appropriate instruments at both the pre- and post-transplantation evaluation.

Actuarial graft and patient survival rates were calculated by life-table analysis, and Gehan's test was used for sta-

tistical comparison.¹⁷ Growth and psychometric data were compared using Student's *t* test.

Results

Between January 1, 1965 and December 31, 1989, 75 infants less than 2 years old underwent 79 transplants (75 primary transplants and 4 retransplants). Of the primary transplants, 23 recipients were 12 months old or younger; 52 were between 12 and 24 months old. There were 63 LRD transplants; 15 CADs; and 1 living unrelated transplant. The latter graft continues to function and is not included in the survival analysis. Patient and graft survival rates for all other primary transplant recipients are shown in Fig. 2. For LRD recipients patient survival at 1 and 5 years was 93% and 82%; for CAD recipients patient survival was 60% and 51% at 1 and 5 years ($p < 0.01$). There was no significant difference in outcome between those children transplanted at age 12 months or younger *versus* those transplanted between the ages of 12 and 24 months (Table 2). When analyzed by etiology of ESRD, oxalosis was associated with decreased patient and graft survival ($p < 0.05$). With an average follow-up of 60 months, 48 infants (64%) are alive with a functioning graft (primary or retransplant).

Effect of Era on Graft Survival

Of the primary transplants, 47 have been performed since 1983: 41 LRD and 6 CAD. Patient survival at 1 and 5 years was 95% and 91%; graft survival was 86% and 73%. Figure 3A shows significantly worse outcome of transplants before 1983 compared to those after 1983 ($p < 0.01$). For non-CSA immunosuppressed patients, there was no difference in survival rate between those transplanted before compared to those transplanted after 1983 (Fig. 3B). Even when high-risk patients (*e.g.*, those with

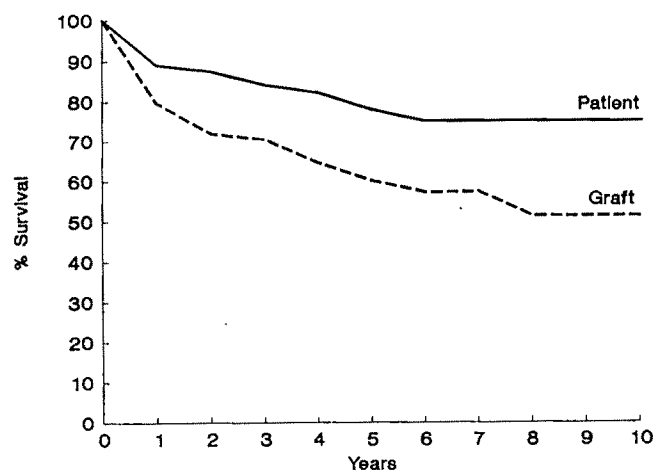


FIG. 2. Patient and graft survival for primary transplants in infants (1965 to 1989).

TABLE 2. Outcome of 74 Primary Kidney Transplants in Infants ≤ 12 Months Versus 12 to 24 Months, by Donor Source

Donor Source, Age at Transplant	% Patient Survival		% Graft Survival	
	1 Year	5 Year	1 Year	5 Year
LRD, ≤ 12 months (n = 18)	100	83	94	71
LRD, 13 to 24 months (n = 44)	90	81	83	63
CAD, ≤ 12 months* (n = 4)	25	25	25	25
CAD, 13 to 24 months (n = 8)	88	72	50	50

* $p < 0.01$ versus LRD ≤ 12 months.

oxalosis) were excluded, there was no improvement of survival rate for non-CSA immunosuppressed patients.

Effect of Immunosuppressive Protocol

CSA was first routinely used in infants at the University of Minnesota in 1984. CSA versus non-CSA patients are compared in Fig. 4. Patient and graft survival significantly improved with CSA ($p < 0.01$). Studying only patients transplanted since 1983, CSA was similarly associated with improved patient and graft survival (Fig. 5) ($p < 0.05$). With CSA patient survival at 1 and 5 years has been 100%, and graft survival is 96% and 82% at 1 and 5 years. For the five CAD transplant recipients on sequential therapy, patient and graft survival rates at 1 year have been 100%.

Parental Donors

Fifty-eight children received primary transplants from a parent (Fig. 6). Patient survival was significantly better in patients receiving a transplant from their father ($p < 0.05$). This difference, seen only in non-CSA infants, was primarily due to a preponderance of maternal donors for infants with oxalosis. With sequential therapy, patient survival from both maternal (n = 10) and paternal (n = 10) donors has been 100%. There was no difference in

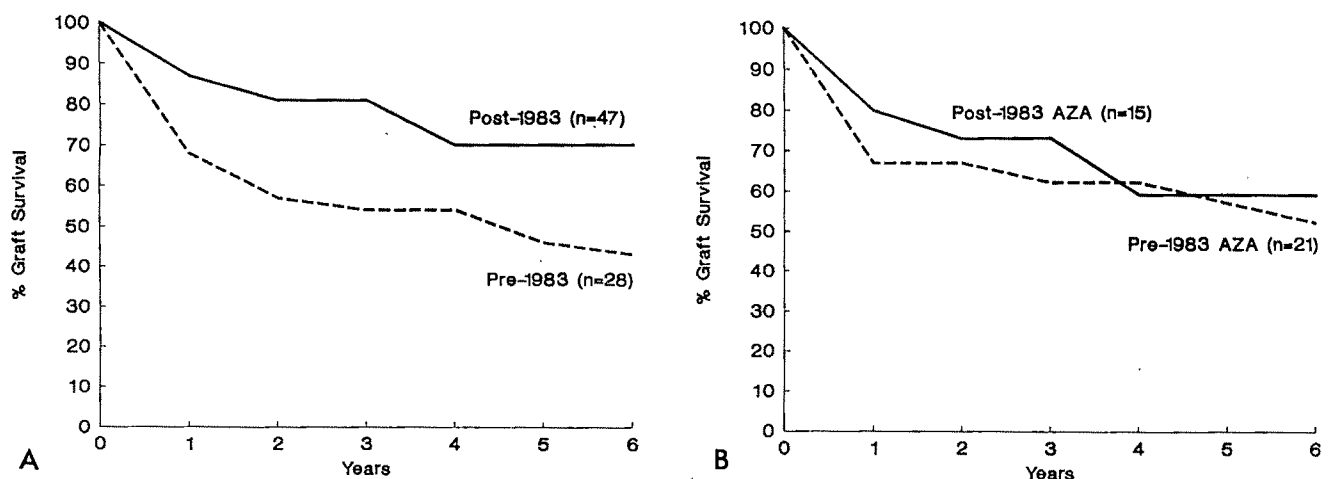
graft survival in recipients of maternal versus paternal kidneys.

Comparison with Older Children

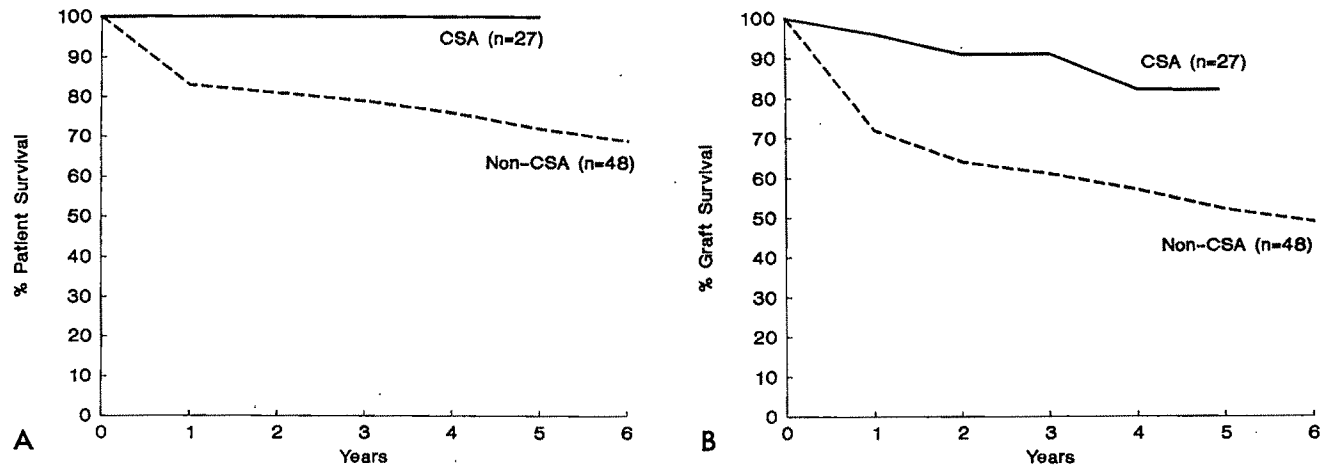
There were no differences in patient or graft survival for primary transplants in infants versus older children (Fig. 7). Considering only non-CSA children, patient survival was significantly better for older children ($p < 0.01$); there was no difference in graft survival. With CSA there were no differences in either patient or graft survival for infants compared to older children. Similarly, when divided into subgroups by recipient age (2 to 5 years, 6 to 10 years, 11 to 15 years, 16 to 18 years), there were no differences in survival rates for infants compared to any subgroup (Table 3).

Retransplants

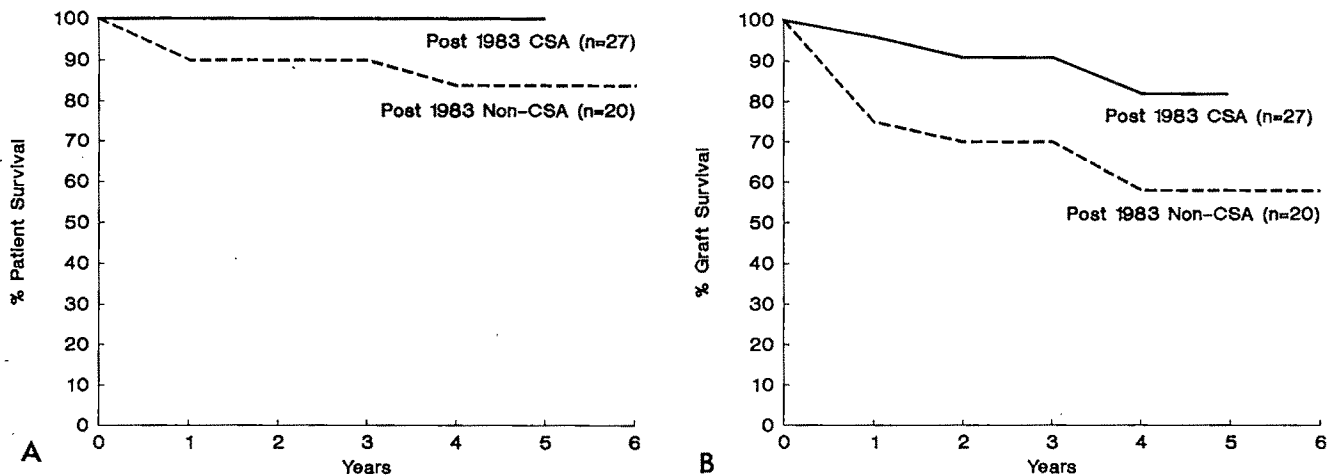
Four infants have undergone retransplantation. The etiology of ESRD was oxalosis in 2, dysplasia in 1, and cortical necrosis secondary to birth trauma in 1. Cause of loss of the primary transplant was recurrent oxalosis in 2, renal vein occlusion with infarction in 1, and sepsis with graft loss in 1. Two of the retransplants were from an LRD and 2 were from a CAD. Two of the patients are



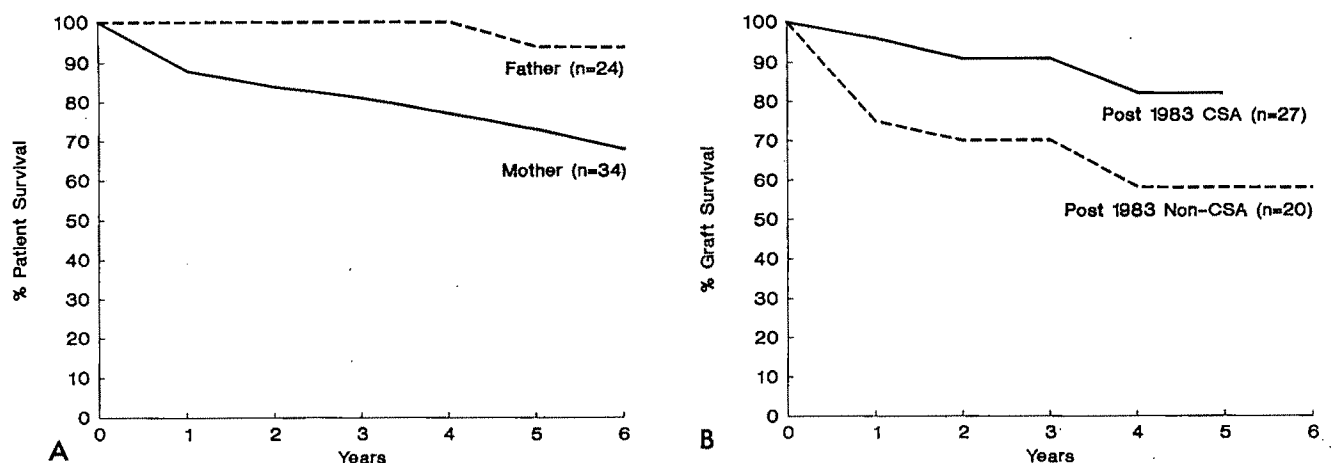
FIGS. 3A and B. Impact of era on outcome. (A) When all infants are compared, outcome after 1983 was significantly better ($p < 0.01$); (B) when only non-cyclosporine-immunosuppressed infants are compared, there is no difference between groups.



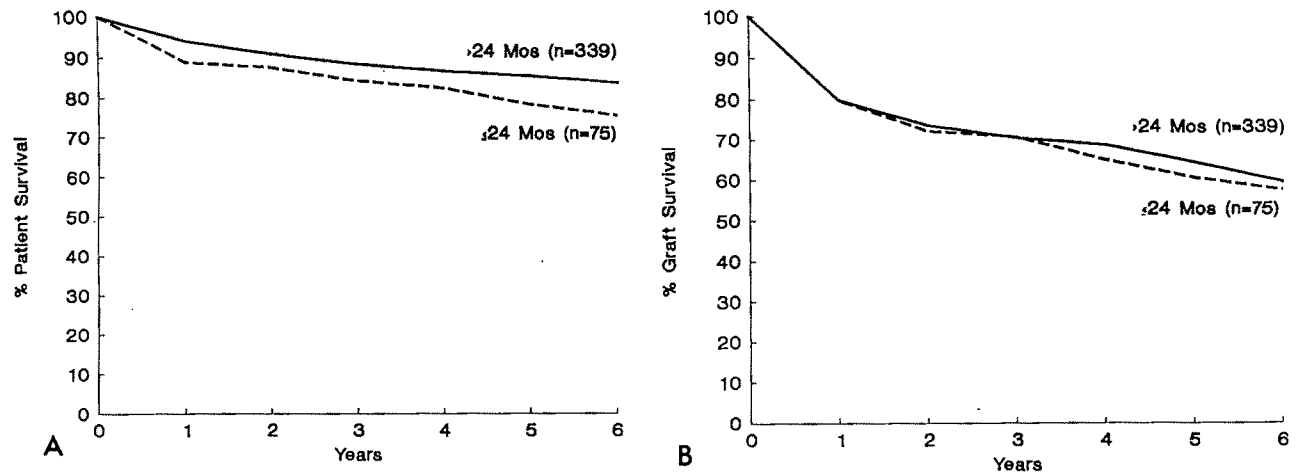
FIGS. 4A and B. Impact of cyclosporine (sequential therapy) on outcome. Patient (A) and graft (B) survival significantly improved in infants receiving cyclosporine ($p < 0.01$).



FIGS. 5A and B. Comparison of cyclosporine (sequential therapy) and non-cyclosporine immunosuppression in infants transplanted since 1983. Cyclosporine was associated with significant improvement in patient (A) and graft (B) survival ($p < 0.05$).



FIGS. 6A and B. Comparison of survival in infants receiving primary transplants from maternal versus paternal donors. (A) Paternal donors were associated with improved patient survival ($p < 0.05$). (B) There was no difference in graft survival.



FIGS. 7A and B. Comparison of outcome in infants (≤ 2 years) versus older children (2 to 17 years). There was no difference in patient (A) or graft (B) survival.

alive with functioning grafts; two died, one from recurrent oxalosis and the other from sepsis.

Cause of Graft Loss

A total of 30 grafts have been lost. Of these, seven were due to death with a functioning graft, including four patients who had undergone pretransplant splenectomy and subsequently developed overwhelming sepsis. Of the remaining 23 grafts, 10 were lost from chronic rejection, 5 from acute rejection, 5 from recurrent disease, and 3 from technical complications. Of the recurrent disease patients, three had recurrent oxalosis. Of the technical complications, 1 was from an acute renal vein thrombosis. Cause of graft loss in infants compared to older children is shown in Table 4. There were no significant differences.

Cause of Death

Sixteen patients died 1 day to 13.9 years after transplantation. This includes the first three infants transplanted, all of whom died from complications of the transplant. They received cadaver kidneys from infants and small children. No further infant transplants were performed until the technique of using adult donor kidneys evolved. Of note, there has not been a death in our infant series since 1983.

A total of 9 patients had septic deaths: 4 from post-splenectomy sepsis (3 pneumococcus, 1 hemophilus influenza), 2 from intra-abdominal sepsis after incidental appendectomy at the time of transplant (a long-since abandoned procedure), 1 from disseminated viral infection, 1 from pneumonia (respiratory syncytial virus), and

TABLE 3. Actuarial Patient and Graft Survival at 1 and 5 Years for Primary Kidney Transplants in Children, by Age at Transplant

	% Patient Survival		% Graft Survival	
	1 Year	5 Year	1 Year	5 Year
All (1965–1989)				
≤ 24 months (n = 75)	88	78	80	60
2–5 years (n = 57)	95	83	77	63
6–10 years (n = 89)	92	87	79	65
11–15 years (n = 115)	94	84	77	63
15–18 years (n = 78)	93	86	86	65
All Cyclosporine (1984–1989)				
≤ 24 months (n = 27)	100	100	96	83
2–5 years (n = 12)	92	92	83	83
6–10 years (n = 16)	100	100	77	77
11–15 years (n = 18)	100	92	94	87
15–18 years (n = 10)	100	100	90	90
Cyclosporine—Living Related Donor				
≤ 24 months (n = 23)	100		96	
2–5 years (n = 6)	100		83	
6–10 years (n = 12)	100		79	
11–15 years (n = 13)	100		100	
15–18 years (n = 6)	100		83	

TABLE 4. Percentage of Graft Loss by Etiology in Children with Primary Kidney Transplants (1965-1989) who Subsequently Lost Graft Function

Etiology	Age at Transplant (Years)				
	≤2	2-5	6-10	11-5	15-18
Technical	10%	7%	21%	5%	0%
Recurrence of primary disease	14%	4%	4%	5%	3%
Acute rejection	17%	15%	16%	18%	8%
Chronic rejection	38%	41%	51%	45%	58%
Death with function	21%	19%	16%	16%	22%
Other	0%	14%	11%	11%	9%

1 from postoperative sepsis and multisystem organ failure. Splenectomy was abandoned in 1984; no patient transplanted since that time has died of overwhelming sepsis.

Of the remaining seven deaths, three were due to recurrent oxalosis. The other four causes were liver failure 16 years after transplantation (a patient with recessive polycystic kidney disease), respiratory asphyxia after aspiration of tube feedings, acute metabolic abnormalities after acute graft loss, and coagulopathy in the immediate perioperative period. Other than an increased incidence of death from the primary disease (oxalosis) in those younger than 2 years, there were no differences in cause of death between those children who were younger than 2 years and older children (Table 5).

Rejection and Function

Of the 79 graft recipients, 53 (67%) have had no documented rejection episodes. Of LRD recipients, 70% have not required anti-rejection treatment and an additional 16% had only a single episode.

For functioning grafts, current mean creatinine level is 0.8 ± 0.2 mg/dL (average, 44 months after transplant). Mean creatinine level for patients having had a rejection episode is 0.9 ± 0.2 versus 0.7 ± 0.1 for those not having had a rejection episode.

Complications

Early. Early complications, including fever and atelectasis, occurred in many of the infants. Also frequent

were abdominal distention and prolonged ileus requiring hyperalimentation.

Chylous ascites occurred in one infant in the early postoperative period. This was documented by abdominal paracentesis with return of lipemic ascitic fluid. This patient was treated with parenteral hyperalimentation for 2 months with complete resolution. Diarrhea in the early postoperative period was common, but rarely of clinical significance. Clostridium difficile colitis occurred in 11 patients. Although most commonly found early in the postoperative period, there has been one case later than 3 months after transplant. All have resolved with intravenous metronidazole or oral vancomycin. There were three cases of graft dysfunction requiring dialysis. Two of these were secondary to biopsy-proved MALG reactions with microangiopathic hemolysis and thrombocytopenia. All three resolved with only supportive treatment. In addition two early urinary leaks required reoperation.

Late. Late complications can be divided into infectious and noninfectious. Noninfectious complications included late small bowel obstruction, ureteral complications, and metabolic abnormalities. Small bowel obstruction occurred in four infants, who were all treated with exploratory laparotomy. The etiology included adhesions in three and intussusception in one. No bowel resections were required, and the postoperative course was uneventful in all four infants.

Two children required ureteral reimplantation, one for distal ureteral stenosis and one for progressive vesicoureteral reflux. Both reimplantations were successful and both

TABLE 5. Percentage of Cause of Death in Children with Primary Kidney Transplants (1965-1989), by Recipient Age

Cause	Age at Transplant (Years)				
	≤2 (n = 75)	2-5 (n = 56)	6-10 (n = 89)	11-15 (n = 115)	15-18 (n = 78)
Alive	79%	82%	79%	74%	80%
Infection	12%	11%	9%	11%	9%
Graft failure	1%	0%	0%	1%	0%
Primary disease	5%*	0%	1%	0%*	1%
Trauma	0%	0%	0%	2%	3%
Malignancy	0%	0%	0%	4%	0%
Cerebrovascular	0%	2%	1%	2%	1%
Other	3%	5%	10%	6%	6%

* $p = 0.01$ when comparing percentage of patients who die because of primary disease versus percentage of patients who die of other causes.

grafts are currently functioning. In addition there were two episodes of obstructive uropathy secondary to hematuria. One episode followed a percutaneous renal biopsy and was treated with a percutaneous nephrostomy tube with preservation of graft function. The second episode was secondary to blunt renal trauma and required placement of a suprapubic tube for decompression. This kidney also maintained function.

Of the 75 patients, 17 have required prolonged anti-hypertensive medication. Of these 17, 16 are well controlled on one- or two-drug therapy. One child has had recurrent episodes of severe hypertension requiring hospitalization. Renal biopsy of this infant revealed severe intrarenal atherosclerosis with renal vascular hypertension as the etiology. Other noninfectious complications have included development of pseudotumor cerebri in 3 infants, hypoglycemic seizures in 9 infants,¹⁸ and enuresis in 2 infants.

By far the most devastating of the late complications has been infection. There were five instances of postsplenectomy sepsis, resulting in death in four patients. All of these children died in a rather short period of time (less than 24 hours); all had been doing exceptionally well with stable creatinine levels.

Recurrent urinary tract infections (UTI) were documented in 15 patients. The usual presenting symptom was fever. The UTIs were frequently treated on an out-patient basis with oral antibiotics. Chicken pox occurred in 17 patients, with no deaths. Documented exposure to chicken pox was treated with prophylactic varicella zoster immune globulin. Now all patients with chicken pox are admitted to the hospital, treated with intravenous acyclovir, and have their immunosuppressive medication modified. Aseptic meningitis has been a rare cause of concern, present in four cases. All resolved without sequelae.

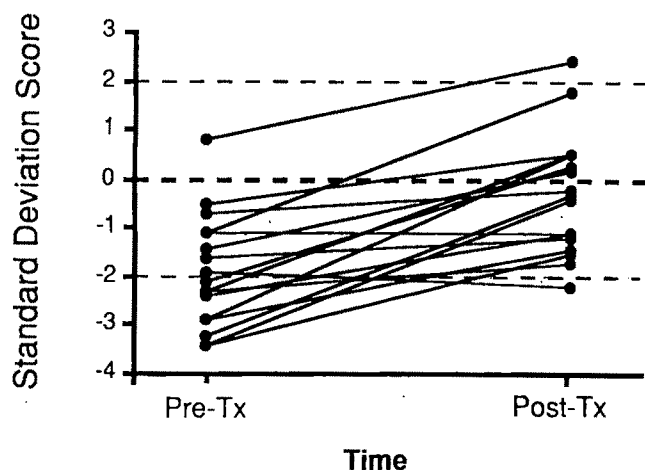


FIG. 8. Standard deviation scores (SDS) for head circumference in 17 infants followed for more than 1 year after transplant. The mean SDS increased ($p < 0.001$); 9 infants showed catch-up growth and moved into the normal range.

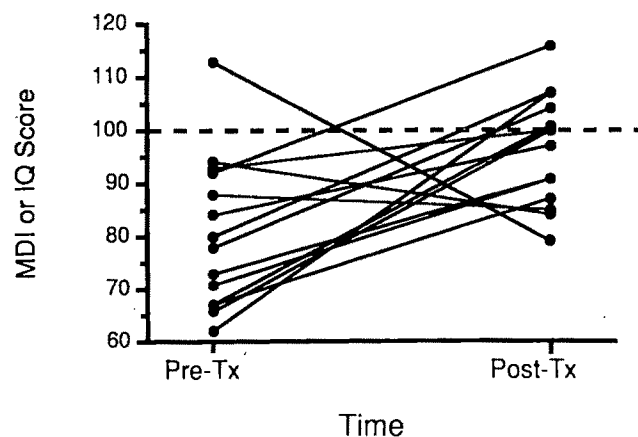


FIG. 9. Cognitive development score or IQ in 14 infants followed for more than 1 year after transplant. Overall there was a significant improvement ($p = 0.013$), with no child more than 2 SD less than the mean.

Growth and Development

Seventeen infants who were younger than 12 months had head circumference (OFC) SDS with a mean value of -1.9 before transplant. But by 1 year after transplant, the mean OFC SDS had increased to -0.3 ($p < 0.001$). All but one patient had scores in the normal range (Fig. 8).

Similarly the Mental Development Index (the Bayley scales) averaged 80.6 in 14 pretransplant infants, but rose to 96.4 after transplant ($p = 0.013$). At follow-up about 1 year after transplant, no child was more than 2 SD less than the mean for cognitive functioning (Fig. 9).

Finally the SDS for length in 17 infants was -2.5 before transplant and only increased to -1.9 ($p = 0.12$) 1 year after transplant (Fig. 10). However, if the three infants with oxalosis are excluded, the values are -2.9 before transplant and -1.7 after transplant ($p = 0.006$).

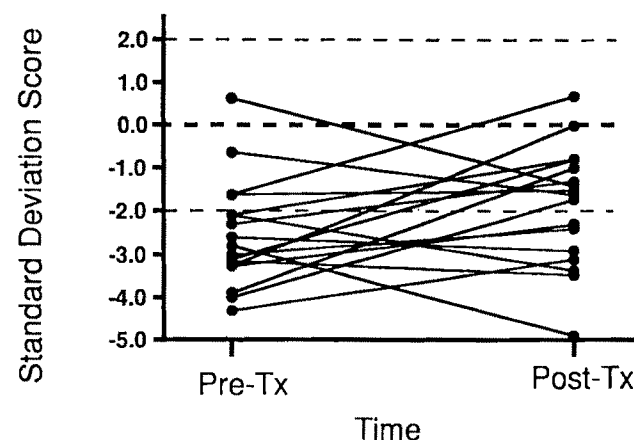


FIG. 10. Standard deviation scores (SDS) for length in 17 infants followed for more than 1 year after transplant. The SDS of 4 infants (3 with oxalosis, 1 with growth hormone deficiency) decreased; 8 had dramatic catch-up growth.

Discussion

Renal failure in infants is not only associated with growth failure and the usual uremic syndromes seen in older children but also has been linked with serious central nervous system (CNS) morbidity, including progressive encephalopathy, developmental delay, acquired microcephaly, and seizures.¹⁹ Such patients require early and aggressive intervention if they are to survive and achieve their developmental potential. National experience with renal transplantation in infants is limited. Since 1965 we have performed 79 transplants in 75 infants who were younger than 2 years. Yet that represents about one quarter of all such transplants done in this country. In fact, in the last decade, 56% of all infant allografts surviving more than 1 year after transplant were transplanted at the University of Minnesota.²⁰ We continue to perform about 25% of the kidney transplants in infants in the United States.

We think that the ability to obtain equivalent patient and graft survival in infants, older children, and adults is highly dependent on an experienced, close-knit team of pediatric nephrologists, transplant surgeons, anesthesiologists, dialysis personnel, transplant nurses, coordinators, dieticians, social workers, and others. As has been previously stated, the infant is not just a small adult; there is a marked difference in the amount of care required. In addition intraperitoneal placement of the relatively large adult donor kidney is associated with a number of management problems. Our approach has been to minimize dialysis therapy in infants because of its inherent complications, difficulties for the family, and expense.¹⁹ When ESRD is imminent, there is no benefit from interposing a dialysis trial between moderate uremia and a kidney transplant. Infants who are at least 6 months of age and weigh 6 kg can be transplanted successfully with adult kidneys.⁹ Bilateral nephrectomy, if necessary, can be done at the time of the transplant (except in patients with severe nephrotic syndrome). With meticulous attention to detail, surgical and postoperative problems can be minimized. Infusing colloid or packed cells (to raise the CVP) and bicarbonate (to neutralize acidosis from the ischemic lower extremities) has helped diminish intraoperative instability.⁹ With careful management, no serious hemodynamic problems have resulted from reperfusion of the relatively large adult kidneys, so we have not seen the high incidence of nontechnical graft thrombosis reported by others.²¹

Similarly, in infants weighing 6 kg or more, there have been no significant difficulties with the intra-abdominal placement of an adult kidney. Abdominal closure can be done without tension, and respiratory compromise has never been a problem. Children on peritoneal dialysis or with huge cystic kidneys have even more capacious ab-

domens; in this situation adult kidneys have been transplanted into children weighing as little as 5.4 kg.

Most earlier reports of renal transplants in infants were discouraging.²¹⁻²⁸ We have found that, with current management, graft survival is equal in all age groups (Tables 2 and 3). The infant's age *per se* should not play a significant part in the transplantation decision-making process. Two major differences distinguish our study from previous reports. First is our preponderance of LRDs (80%). The ethics and propriety of LRD in this situation have been questioned, particularly because the long-term outlook for the transplanted kidney is undefined⁴; yet the results of our study support their use. Since 1983, with our current protocols, infant survival at 1 and 5 years is 100% and graft survival is 96% and 82%, results unequaled by other forms of renal replacement therapy (Fig. 5). There is no difference in graft survival in recipients of maternal compared to paternal kidneys, suggesting that, with current immunosuppression, noninherited maternal antigens are not important in outcome of LRD transplants. Mean serum creatinine level in those with functioning grafts is 0.8 ± 0.2 mg/dL.

In all age groups living related donation continues to be the most important predictor of long-term renal allograft function.²⁹ However, with sequential therapy, there also has been an improvement in results for our CAD recipients: 100% patient and graft survival at 1 year. This is in marked contrast to the recent report by Arbus et al.³⁰ of 33% cadaver graft survival at 1 year in recipients younger than 3 years. In Arbus's series, 44% of the patients lost their grafts to primary nonfunction, thrombosis, and other technical complications. Based on their experience, the authors questioned the cost-effectiveness of cadaver transplants in young children. It was unclear how many of these patients received CSA. In fact, we as well as others^{31,32} have shown marked improvement in results of cadaver transplantation in young children who received CSA.

A second major difference between our study and previous reports is the immunosuppressive protocol. All infants at our institution receive a 2-week course of MALG. It is unusual for a rejection episode to develop while prophylactic MALG is administered. This provides a rejection-free window for recovery from the operation, allows the transplanted kidney to begin functioning normally, and thus decreases the potential diagnostic dilemmas during this period.¹⁵ In addition MALG allows us to delay CSA immunosuppression until normal renal function returns. At discharge all infants are maintained on prednisone, azathioprine, and CSA. This sequential immunosuppressive protocol has been associated with improved results (Fig. 5) in our series as well as others.^{31,32}

We wish to emphasize that our patients were not free

of complications. Most infants had at least one complication before discharge. An unusual problem in our infants, compared to older children and adults, was a period of immediate postoperative oliguria after revascularization of the transplant.⁹ Frequently a significant diuresis began 6 to 8 hours after transplantation. It is important to recognize this pattern. Patience is required, for if too vigorous an attempt is made to induce a diuresis by fluid administration, significant hypertension and/or pulmonary edema may develop.

Fever, diarrhea, and/or feeding difficulties were frequent but usually resolved spontaneously. *Clostridium difficile* colitis occurs in a significant number of patients. Its recent increased recognition is probably due to frequent antibiotic use and to improved diagnostic techniques in the last few years.

Persistent postoperative fevers with no definable etiology caused considerable concern. The differential diagnoses include, in addition to the usual causes of postoperative fever, rejection.¹⁵ By far the most difficult diagnosis to make in the early postoperative period is early rejection during MALG therapy. Evaluation consists of ultrasound to rule out obstruction and renogram to discover possible urinary leak. If rejection remains a possibility, percutaneous biopsy is performed as the definitive diagnostic test. Notable elevation of creatinine is a relatively late sign due to the large functional reserve of the adult kidney and the small muscle mass of the infant.

Other complications in the early postoperative period included prolonged oliguria requiring dialysis, and MALG reactions requiring a switch to OKT3.

Viral disease remains a significant problem in the later postoperative period. There have been two pulmonary deaths of viral etiology, including one from respiratory syncytial virus. Chicken pox has occurred in 17 of the 75 patients. Treatment consisted of temporarily discontinuing azathioprine and administering intravenous acyclovir. This approach has resulted in no mortality and no episodes of graft rejection. Reported exposure to chicken pox is treated with varicella zoster immunoglobulin.

Late bacterial infection also has been a significant post-transplant problem leading to graft loss (death with function). With the 1984 finding of no significant improvement in survival with pretransplant splenectomy and a high rate of postsplenectomy sepsis, routine splenectomy was abandoned.¹³ Since then we have had no deaths from overwhelming sepsis.

The major cause of graft loss remains rejection, either acute or chronic. In addition certain diseases have a high incidence of recurrence. Transplant recipients with oxalosis continue to have a high rate of disease recurrence and graft failure. Of the eight infants transplanted for oxalosis, three have died from progressive disease. Of the

remaining five patients, two have required retransplants; another has evidence of recurrence on biopsy but a functioning graft at this time. Although oxalosis remains a challenging disease to treat by renal transplantation, it should be clear that the alternative is death.⁷ The role of liver transplantation in these infants has not been adequately determined.

It has long been recognized that infants and children with uremia do not grow normally.³³ Betts and Magrath³⁴ first reported growth patterns in infants with renal insufficiency. At birth height was normal or subnormal, but linear growth was subsequently poor, with a loss of about 2 SD by 6 months of age. In addition Rotundo et al.³⁵ demonstrated a progressive encephalopathy in 20 of 23 infants with renal insufficiency. This was characterized by a marked delay in attaining developmental milestones and the appearance of seizures, dyskinesia, and hypotonia; these symptoms were associated with acquired microcephaly. The association of impaired neurologic development and chronic renal failure from infancy recently was reviewed by Polinsky et al.³⁶

Dialysis has not been shown to be typically associated with accelerated or catch-up growth or reversal of developmental delay.³⁶ Kleinknecht et al.³⁷ reported that, in prepubertal children on hemodialysis for at least 1 year, one third had normal growth compared to children of similar age. However these patients had previous growth retardation and might have been expected (under normal circumstances) to show an accelerated growth rate. One third had a moderately reduced growth rate and one third had severe growth failure. For children younger than 3 years, there was a dramatically reduced growth rate during the first months of therapy. Bird and Semmler³⁸ studied 10 children with renal insufficiency at birth who were started on peritoneal dialysis during the first 3 months of life. At the time of testing (less than 24 months), all children showed significant delays in both cognitive and motor development.

Growth after successful transplantation is better than that seen with dialysis. The European Dialysis and Transplant Association reported that growth velocity was significantly better in prepubertal children after transplant (4 cm/year) than on dialysis (2 cm/year).³⁹ In addition, after a 5-year period of treatment, prepubertal children lost significantly more SD from the mean on dialysis (2.3 SD) than after transplantation (0.4 SD). However growth potential appears to depend on the age at transplantation.^{40,41} Ingelfinger et al.⁴¹ reported that successful transplantation was associated with improved growth in children younger than 7 years; children older than 7 years did not have the same growth acceleration after transplantation. Similar accelerated growth was noted by Ettenger et al.⁴² in patients younger than 9 years at trans-

plantation; however this pattern occurred only in those with a low steroid dose (< 0.24 mg/kg/day) and excellent renal function (creatinine clearance ≥ 89 mL/min/1.73 m²). We reported⁴³ on serial measurements in infants younger than 12 months at transplantation. Those without oxalosis, feeding problems, or chronic rejection showed accelerated statural growth; most achieved normal head circumference and normal or improved neuropsychologic development after transplantation.

Perhaps even more important than linear growth is the impact of uremia on the developing CNS in infancy.^{35,44} McGraw and Haka-Ikse⁴⁴ studied 12 children who had chronic renal failure from infancy and underwent dialysis at a mean age of 18 months and transplantation at a mean age of 28 months. Head circumference in all 12 children was within the normal range at birth, but by 1 year it was more than 2 SD less than the mean in 9, and more than 3 SD less than the mean in 6. Ten patients underwent developmental examination at least once; 8 had moderate to severe gross motor delay, 9 had language delay, 9 had delayed cognitive and fine motor skills, and 7 had delayed psychosocial skills.

Our review of growth is retrospective and some data is incomplete; some patients have died or lost graft function. However the data for the youngest children (younger than 12 months) is the most compelling and the most complete. In this group we have seen unequivocal improvement in head size, development, and linear growth. Previous studies have documented acquired microcephaly developing during ESRD in very young children.^{32,33,41} This complication looms particularly ominous when it is recognized that head circumference is directly related to brain size, composition, and weight⁴⁵ as well as later IQ.⁴⁶ While the role of time as a fourth dimension⁴⁷ in ESRD is unclear, normally more than 85% of growth in head size has occurred by 12 months of age, suggesting the existence of an undefined critical period for effective intervention early in infancy. In this regard only one transplanted infant (a premature twin) had an OFC less than -2 SD at follow-up. Dramatically the nine infants with microcephaly at transplantation showed 'catch-up' head growth and moved into the normal range.

Regardless of theoretical questions, the functional consequences of successful transplantation in these young children are also clear. The serial comparison of cognitive development shows a significant improvement in score after transplantation (Fig. 9), averaging 16 points. Eight of the fourteen infants improved their scores, so that all but one tested within 1 SD of the mean. The one child with a significant decrease remained in the normal range and has not been retested. Finally the increase in length seen even in the first year after transplantation has been consistent. Although the statistics are not impressive, ex-

amination of the data (Fig. 10) reveals that at least 8 of the 17 infants experienced 'catch-up' growth, growing at velocities greater than normal infants of the same age. Of the four infants with the most marked decline in SDS, three suffered systemic oxalosis and one has documented growth hormone deficiency.

While this data includes only infants younger than 12 months, another study in our transplant population shows comparable results in a recent cohort of 37 children who were younger than 30 months at transplantation.⁴⁸ In these children mental development scores improved from 80 before transplant to 91 after transplant ($p < 0.05$). Corresponding pre- and post-transplant values for the OFC SDS were -2.1 and -0.8 ($p < 0.025$), while the mean height SDS increased by 0.7 ($p < 0.025$).

The results of renal transplantation in children have improved steadily. Associated with this improvement has been the willingness to offer transplantation to progressively younger children and infants. Still considerable controversy has existed as to whether any form of renal replacement therapy should be provided for these children. It has been argued that the results do not justify the physical and emotional stress to the family. At best it is unknown what the long-term results will be.

We have shown that transplants in infants younger than 2 years can be done with the same patient and graft survival rates as in older children and adults. With an average follow-up of 60 months, 64% are alive with functioning grafts. Patients with successful transplants have improved growth and development with excellent rehabilitation. Thus we see no reason to discriminate against transplantation for children who weigh at least 6 kg, or to chronically maintain them on dialysis until they are bigger and stronger.

Our present results allow us to unhesitatingly recommend early transplantation as the preferred method of treatment of ESRD in infants. We prefer LRDs but believe CAD transplants should be promptly performed when LRDs are unavailable. As described above a prerequisite for successful transplantation in infants and small children is a close-knit team, excellent communication, and well-established protocols.

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DISCUSSION

DR. OSCAR SALVATIERRA (San Francisco, California): Dr. Najarian's paper can best be placed in perspective by recognizing that very few renal transplants have been performed in infants and small children. Prior to 1980, infants and small children with end-stage renal failure were generally not considered candidates for renal transplantation, and only selected patients were considered for dialysis. Currently infants and small children are being treated in greater numbers, but many pediatric nephrologists appear to consider peritoneal dialysis, not renal transplantation, as the primary therapy of choice in these patients.

It is in this environment that Dr. Najarian has spearheaded renal transplantation in this pediatric group, accumulating the largest such series of 79 transplants.

The procedures are often difficult, require meticulous surgical technique, and in addition an integrated team approach for these patients. Complications in this patient population can be disastrous. However, renal transplantation properly carried out can result in the excellent outcomes reported today with restoration of normal life, growth, and development to these infants and small children. This contrasts with cul-de-sac-like therapy of peritoneal dialysis in this patient population where growth retardation, poor nutrition, microcephaly, progressive central nervous system morbidity, skeletal deformity, recurrent peritonitis, endless hospital stays, exorbitant costs and often death characterized the course of many patients.

At UCSF we have performed 35 transplants in infants and small children weighing between 5 and 15 kg, with results similar to Dr. Najarian's. Seventeen patients had parental donors and 20 were given cadaveric grafts. In the living related group, graft survival has been 94% and 86% at 2 and 5 years, with patient survival of 94% at 5 years.

In the cadaveric group treated with cyclosporine sequential therapy, graft survival has been 85% at both 2 and 5 years, while patient survival is 93% at 5 years.

In contrast to Dr. Najarian's series, where transplantation has been generally carried out before most patients reach dialysis, in our series many patients come to transplantation on peritoneal dialysis, in sub-optimal nutritional status, and with moderate to severe abdominal adhesions from recurrent bouts of peritonitis.

There are also a number of patients who would have been good candidates for transplantation who have succumbed on peritoneal dialysis before renal transplantation was made available to them.

I therefore strongly support Dr. Najarian's recommendation that renal transplantation should be carried out when end-stage renal failure is imminent. There is no benefit from interposing a dialysis trial between moderate uremia and a kidney transplant. Long-term dialysis can only lead to potential compromise of a later renal transplant, and if not, actual noncandidacy or death of the infant and small child.

Dr. Najarian, I think you would support the thesis that this scenario is currently no longer acceptable.

I think this is also consistent with what well-informed parents would want for their child.

DR. JEREMIAH TURCOTTE (Ann Arbor, Michigan): As Dr. Salvatierra mentioned, this experience with kidney transplants in infants is one of the most successful and probably the largest in the world.

First, should related or cadaveric donors be used in these infants? This series definitely demonstrates that excellent results can be obtained with related donors. However, the number of cadaveric transplants is too few, that is 15, to draw conclusions about this category of transplants. The results, however, are encouraging in that the five most recent recipients of cadaveric transplants in his series, which were treated with quadruple, sequential immunotherapy, had a 100% 1-year survival. We also use and have had excellent results with sequential, quadruple therapy for both related and cadaveric transplants in both infants and adults.

Another very important issue is whether growth and mental development will proceed normally or accelerate after transplantation. As you saw in this report, his answer is 'yes' to this, and it confirms our own results.

This slide shows improved standard deviation scores for growth in nine children with an average age of 4.4 years. However, if one delays transplantation until the age of 7 or 9 years, accelerated growth is not seen nearly as often.

A key question is whether all infants with renal failure should be transplanted promptly. In our experience, with refinements in the technique of peritoneal dialysis, better nutrition, and avoidance of aluminum toxicity, which caused mental retardation in the earlier years of dialysis, many infants can be maintained for months to several years with good long-term results and without loss of growth or mental capacity.

The most important point is that the transplant surgeon should see these patients at the time that they are put on dialysis, and if they are not doing well, they should be transplanted promptly. So we would prefer to see how they do on dialysis, intervene when necessary, but not routinely transplant them at a very young age. Keep in mind that most series of transplants in this age group do not show as good results under the age of 2 years, and of course, most series have not used related donors to the same extent as the series reported today.

Dr. Najarian, should we always use adult kidneys in infants, as results seem to be better with this combination? This is an issue that the United Network for Organ Sharing is discussing in relation to allocation policies for kidneys.

DR. ARNOLD G. DIETHELM (Birmingham, Alabama): This is an unusual population of patients under the age of 2 years and a far greater experience than has been published to date.

I would like to ask Dr. Najarian several technical questions that we have found to be important.

First the placement of an adult kidney in an infant creates a large AV shunt. What attention to detail do you place at the time of unclamping the vessels, particularly to the effects of unclamping the distal artery and vein, and in what sequence? How do you maintain adequate systolic arterial pressure during and after declamping?

The second comment pertains to the point in your manuscript where you rewarm the kidney with saline just prior to unclamping. We have never done that, and it has always impressed me that warm blood can flow into a cold kidney with few or no complications.

Last I would like to raise a point related to the use of CAPD after rejection. I recognize that you had a few irreversible rejections, but we have used CAPD for a year or two after rejection while waiting for cadaveric organs and found that children were able to grow during that period.

A comment about the related living donor: In our part of the country, where the black race has a large incidence of hypertension within the family, living related donors are not often available, and we have used CAPD for a year or two with better results than we would have expected.

DR. THOMAS E. STARZL (Pittsburgh, Pennsylvania): This marvelous 20-year experience has emphasized again the durability of pediatric recipients as well as the superiority of living related donors who were used in more than 80% of their cases. I once performed living donor transplantations and can affirm from our early experience much of what John has said.

Last spring I was asked by a nephrology organization to find the world's kidney transplant survivors treated before early 1964, of course, excluding identical twins. There were only 24 in the world, all but nine from our original Colorado program (Starzl TE, Schroter GPJ, Hartmann NJ, Barfield N, Taylor P, Mangan TL: Long-term (25-year) survival after renal homotransplantation—The world experience, *Transplant Proc*, In press). This was the series that John Mannick mentioned yesterday. These six centers, which you see listed here, contributed the other nine cases: Boston, Cleveland, Paris, and Edinburgh (one each), three by Dave Hume, and two from the original Minnesota program run by Rich Lillehei and Bill Kelly. Of the 15 Colorado patients who have survived for 26 to 29 years, ten were infants or children. Most of the donors were parents, as we have heard in this series today. Four of our original pediatric patients died within the first year, bringing the group down from 16 to 12, but further deaths did not occur until 11½ and 14½ years. Thus, the 26- to 29-year pediatric survival in this group is still 63%.

Another point worth mentioning is that all 24 of the world's survivors from this antediluvian era were recipients who received living related kidneys. As of last summer, there was not a single example in the world of a 25-year survival with a cadaveric kidney or even with non-related living donor kidneys.

This fact and other data presented today by Dr. Najarian reemphasize that the great challenge in transplantation is to perfect or at least improve cadaver transplantation, and it is only fair to point out that this consideration probably is what has put off the nephrologists in their decision of the kind of care selected for their children.

I am pretty sure after talking to John, that the smallest of our pediatric patients of that era were probably the size of Najarian's largest patients, and this, of course, is an acknowledgement of Najarian's technical mastery. We realized early in our pediatric experience that an intra-abdominal operation often would be necessary to allow placement of adult kidneys into tiny recipients. This procedure, which you see here, was described in 1964 (*Surg. Gynecol Obstet* 119:106, 1964) and became the mainstay approach for adult to child transplantation as we have heard so brilliantly described today.

I have really only one question for Dr. Najarian. You have now been able to follow many living donors for a number of years. I once had a terrible accident with a living donor in which a professional athlete lost her foot after an aortogram on another service and have never been able to bring myself to do a living donor operation again. I wonder if you could tell us in the course of your donor work-up, donor nephrectomy, and later follow-up, if any of these donors have died, experienced any complications, or other late sequelae of which you have personal knowledge.

DR. JOHN S. NAJARIAN (Closing discussion): I want to thank the four discussants for their kind remarks and for their interest in what, I think, is the very important field of renal transplantation in infants.

Oscar Salvatierra summarized the data from San Francisco very well, and we would agree with what he says. One of the problems that all of us face is dealing with our pediatric nephrologists. They are reluctant to give these patients up, and under these circumstances they sometimes wait too long. As Oscar said, when he gets his patients, they are on peritoneal dialysis, and often not in the best of shape. We used to see the same patients, Oscar, although I think we are fortunate to have a very enlightened group of pediatric nephrologists.

The next comment was made by Dr. Turcotte, who was talking about children older than 2 years. As he mentioned, we have only done 15 cadaver transplants. The truth is that more recently our cadaver transplants in children are doing very well. As a matter of fact, I don't think we have lost one in recent years. Primarily we use sequential therapy, which gives us a window of opportunity on ALG so that we don't have to begin to treat these children with triple therapy for the first week. In other words, we add their cyclosporine only after they have adequate urine output and are doing well, with good renal function.

However I would really strongly disagree, Jerry, with waiting to transplant children until they have grown. In every series I have ever seen where they have continued to dialyze infants—specifically under age 2—their head circumference has not grown. When their heads don't grow, mental retardation follows. This has been shown over and over again. Thus, if at all possible, I think one should try to convince the pediatric nephrologist that these infants should be transplanted as soon as surgically feasible—usually the first year of life.

Should we always use adult kidneys in children? No, we use children's kidneys quite often. Adult kidneys are used because they are often all that is available for infants when you are looking for living related donors. Thus, only parents are available sources for most infants, who do not

usually have siblings old enough to be donors. If no related donors are available, then adults and young children are used as cadaver donors.

Again I appreciate Dr. Diethelm's remarks. He asked some specific questions about technique. The first had to do with the use of adult kidneys in infants. Yes, the adult kidney becomes a large AV fistula. In addition, you clamp off the aorta, so as soon as you unclamp, you perfuse both legs and this huge kidney. This becomes quite a load. You must prepare the infant for the consequences of this sudden large drain of blood volume. We anticipate this drop in blood pressure by increasing the CVP with blood and fluid replacement. We elevate the CVP to around 20. The infants then really have a full 'tank.' Now when we declamp there is only a minimal fall of blood pressure. We get some fall, but it is very minimal. This is a very important point, and you should not just use active pharmacologic agents to control the blood pressure. It must be done with fluid and volume replacement. Under these circumstances the kidneys will perfuse very nicely and you won't get a declamping problem.

We do rewarm the kidneys just before we unclamp. We keep the kidneys cold until we unclamp, but warm them before reperfusion to avoid systemic hypothermia in the infant.

We use CAPD if necessary, following rejection, or if we have to hold the infant on dialysis until another transplant donor can be found. Infants respond very well to chronic peritoneal dialysis, but only as a holding pattern, and we transplant them as quickly as possible.

Finally, Dr. Starzl, I was delighted to hear your results from your bellwether series, the 64 patients that were transplanted with living related and cadaver donors. This important series was the stimulus that convinced many of us to start clinical renal transplant programs. It is nice to know some of these patients are alive and well over 25 years later. I think the children in that group were not the infants we are talking about today, as you indicated. However this series shows very nicely the longevity that can occur with living related transplants. We can get excellent survival at 1 year, 2 years, and 5 years with cadaver renal transplantation, and in many series the cadaver results approach those of related renal donors. However, if you go out as far as 10 years and follow the straight line attrition posttransplant, the results begin to separate. Paul Terasaki has shown very clearly with semilog graphs that the slope of cadaver renal transplants demonstrated a half-life of 7.7 years compared with 11 years with living related donors. Thus, if longevity is what we are looking for, then living related donors should still be the first priority, at least with current immunosuppressive therapy.

I was sorry to hear about Dr. Starzl's mishap with the living donor. I could see how that could prejudice your attitude regarding the use of living donors. We have been very fortunate. In more than 2000 living related kidney donors, we have never had a death or serious complication. Of course, we are going to experience such a tragedy someday. You can't keep doing major surgery and not experience such an unfortunate complication eventually, but so far it has not happened to us. I feel this is true because of the careful attention paid to the donor workup and the donor operation.

We have also now done some 75 living related pancreas transplants, and have not had any serious complications in those patients either. But I do think you have to take extra special precautions. The living related donor is our primary concern. That is where our priorities are—not with the recipient, but with the healthy living donor. As a result, if you are very careful in working these donors up and pay very careful attention to them it is possible to reduce complications to an absolute minimum.

Application of Reduced-size Liver Transplants as Split Grafts, Auxiliary Orthotopic Grafts, and Living Related Segmental Transplants

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The University of Chicago program in pediatric liver transplantation continues actively to seek innovative surgical solutions to problems related to the management of children with end-stage liver disease. Among the most important problems facing these children is a shortage of donor organs, which results from three factors in addition to the actual supply of pediatric donors: the concentration of pediatric liver disease in the population younger than 2 years; the necessity for a graft that is small enough; and the epidemiology of accidents and other events that lead to organ donation. Transplantation using a liver lobe as a graft overcomes size disparity and shifts the available supply of organs from older donors to younger recipients. This work describes the technical aspects of recent innovations in the use of liver lobes in pediatric transplantation, simple reduced-size liver transplantation (RLT), split-liver transplantation (SLT), orthotopic auxiliary liver grafting (ALT), and transplantation using a living related donor (LRLT), and compares their results. Since November 1986 a total of 61 procedures have been performed in which a liver lobe was used as a graft: 26 RLT; 30 SLT, 25 in children and 5 in adults; 5 LRLT; and 1 ALT. Overall 62% of transplants performed in children have involved using a liver lobe as a graft. The rates of complications are somewhat higher than with whole-liver transplantation, but this may not be entirely the result of the complex procedures. Split liver transplantation is associated with the highest mortality and complication rates. Living related liver transplantation has been associated with complications in donors and recipients, but to date survival is 100%. Orthotopic auxiliary liver transplantation effectively corrected the metabolic defect in one patient with ornithine transcarbamylase deficiency. Overall the various modalities of using graft reduction have resulted in postoperative results similar to those achieved with full-size grafts, while pretransplantation mortality has been limited to less than 2%. Thus the use of grafts as liver lobes accomplishes the goal of reducing global mortality among children with end-stage liver disease, but at the cost of increased surgical complexity and more postoperative complications.

THE AVAILABILITY OF donor organs is a critical factor that limits the use of orthotopic liver transplantation (OLT), particularly in children. Pres-

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ently the supply of cadaveric organs is marginally adequate for adult candidates for OLT, but the supply of pediatric donor organs remains insufficient. The past few years have seen no significant increases in the cadaveric organ supply, despite improved organization of the organ procurement system and supportive legislation. At the same time, liver use has increased steadily as a result of widening awareness of the indications and favorable results of OLT and the proliferation of transplantation centers.^{1,2}

When considering the limited supply of donor organs for children, three factors appear to be important in addition to the finite supply of pediatric donors: the epidemiology of pediatric liver disease, which concentrates the need for OLT in the population younger than 2 years; the necessity for a graft that is small enough to fit into the hepatic fossa and to be adequately perfused; and the epidemiology of accidents and other events that lead to organ donation, which spreads the supply of donors to all children with no focus in the younger population.^{3,4} Because there is a need for several hundred OLTs per year to be performed in children, there is a clear call for maximum use of the available organs. Reduced-size liver transplantation (RLT), in which only a lobe of the liver is used as a graft, overcomes size disparity and shifts the available supply of organs from older donors to younger recipients.

Reduced-size liver transplantation was performed initially in a child by Bismuth and Houssin⁵ and Broelsch et al.,⁶ demonstrating the technical feasibility of the procedure. We published the first series of RLT in this country⁷ and demonstrated that reduction in preoperative mortality rate is a major advantage of a strategy for pediatric transplantation that includes RLT. Recently we published the first series³ in which RLT was used as a routine therapy in children, which demonstrated that postoperative survival was identical for recipients of RLT and full-size OLT while waiting-list deaths virtually were

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eliminated. Similar results have been reported in Western Europe.⁸ Since then RLT has become a standard therapy for small children needing liver transplantation in the United States, Europe, and Australia.^{3,8-10}

The use of RLT to overcome size disparity in a single recipient is only an initial step in the application of the concept of grafting hepatic lobes into children. Split-liver transplantation (SLT), in which two recipients receive grafts from a single donor, is based on the fact that one potentially usable lobe is discarded during the RLT procedure. Pichlmayr et al.¹¹ reported the initial success of the SLT procedure. We performed a series¹² of SLTs and reported preliminary results in nine pairs of recipients. Subsequently SLT has become the preferred procedure at the University of Chicago, if the donor organ permits and two appropriate recipients can be identified. Here we report the technical considerations of SLT and the results of our expanded series.

Two additional advances that make use of the technical gains achieved during the performance of RLT and SLT are the use of a liver lobe as an auxiliary liver graft (ALT) for the treatment of metabolic disease and transplantation using living donors (LDLT), both of which we have accomplished.

The present report documents the results accomplished with extension of the concept of RLT in our program. We present techniques, results, and complications with three procedures (SLT, ALT, and LRLT) placed in perspective with results of standard OLT and RLT during the same period. Particular attention is given to technical refinements that have occurred as our experience increased.

Patients and Methods

Experience with Liver Lobes Used as Hepatic Allografts

A total of 331 liver transplants were performed at the University of Chicago between November 1984 and February 1990. Before November 1986 RLT was used only in emergency situations. The results reported here refer to the period since November 1986, when RLT was adopted as routine strategy in the management of children in our institution, as reported previously.³ During this period 61 procedures were performed in which a liver lobe was used as a graft. Twenty-six RLTs have been performed since November 1986. Since July 1988 we performed SLTs in 30 recipients, 25 children and five adults. Since November 1989 LRLTs have been performed in five patients. A single ALT was performed in September 1989, with the graft coming from a SLT procedure. Overall 62% of transplants performed in children younger than 2 years since November 1986 have involved a liver lobe used as a graft.

Split-liver Transplantation: Indications and Technical Considerations

Decision making for SLT is complex and has evolved with increasing experience. Generally recipient pairs have included one critically ill and one medically stable recipient. Anatomic criteria for acceptance of the graft have been the absence of any vascular anomalies and an appropriate size match for a larger recipient of the right lobe. Depending on the size disparity, a smaller recipient received either the left lobe (segments 2, 3, and 4) or left lateral lobe (segments 2 and 3). The strictest of donor selection criteria were used to assure organ quality because primary nonfunction due to graft ischemia would jeopardize two recipients.

The predominant diagnosis for recipients of SLT was biliary atresia ($n = 16$). The procedure was also performed for fulminant liver failure ($n = 8$) due to non-A, non-B hepatitis ($n = 4$) or transplant failure ($n = 4$), due in two cases to arterial thrombosis and in two to primary non-functioning grafts. Cirrhosis, associated with metabolic disease in two cases, accounted for the remaining patients ($n = 6$).

We have described previously the procedures for the preparation of SLT.¹² The donor liver is obtained by standard techniques of multiorgan procurement. The preparation of the two grafts is performed in the recipient operating room. *Ex vivo* hepatic resection is performed by passing through the principal fissure between the right and the left lobe (Fig. 1). Dissection of the hilar structures is carried into the parenchyma, dividing the portal vein and hepatic artery at their primary bifurcation, with the right lobe receiving the full length of the portal vein and the common hepatic artery. The right hepatic duct is preserved beyond the junction of the left duct, which is severed with suture ligation of the site of transection. The vena cava is maintained in continuity with the right lobe, with the caudate lobe removed. Hepatic venous outflow from the right lobe remains unchanged and the implantation is essentially the same as with a full-size transplant, with the right lobe fitting into the right subdiaphragmatic space. Dissected surfaces are meticulously suture ligated and, after reperfusion, sealed with fibrin glue and/or surface coagulation.

The left graft is prepared for the smaller recipient by using segments 2, 3, and 4, when pediatric livers are used, or segments 2 and 3 when the size disparity is greater. In either case vascular reconstructions are performed using donor iliac arteries or veins to extend the vessels, as we have previously described.¹² Discarding segment 4 when preparing a left lateral lobe (segment 2, 3) graft from the left lobe provides more length on the artery and portal vein, and the need for vascular interposition can be

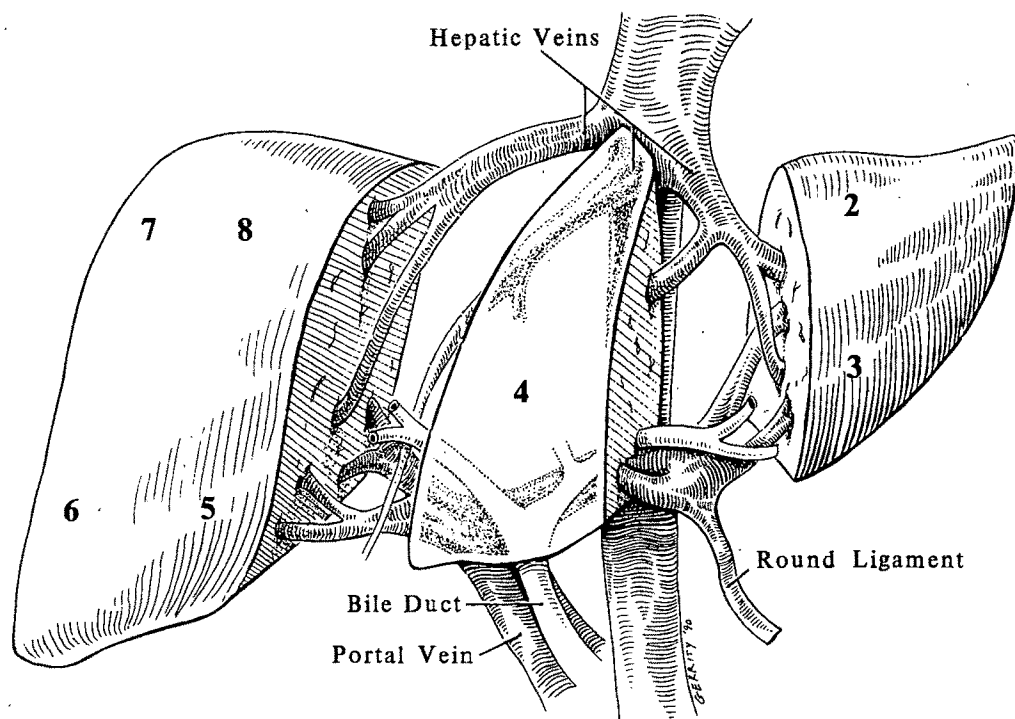


FIG. 1. A simplified schema of the intrahepatic anatomy is depicted. For clarity the arterial structures have been omitted. Most important is the location of the junction of the bile ducts to segments 2, 3, and 4. If the liver is transected to the left of the round ligament, two separate biliary orifices (segments 2 and 3) will be encountered. This has technical implications for both SLT and LRLT.

avoided. Also in segment 2, 3 grafts, reconstruction of the recipient vena cava can be facilitated by preparing the middle hepatic vein as a vascular interposition. Alternatively the left hepatic vein can be anastomosed end-to-side to the isolated recipient inferior vena cava.¹³ The cut surface of segment 2, 3 grafts is significantly reduced, which reduces problems with bleeding.

Auxiliary Orthotopic Liver Transplant Procedure

We treated a 14-month-old patient with ornithine transcarbamylase (OTC) deficiency, a urea cycle defect, with a segment 2, 3 graft placed as an auxiliary graft in an orthotopic position. Liver replacement was avoided because the native liver was functional, except for the inability to metabolize ammonia, and was not cirrhotic. We reasoned that the auxiliary lobe graft would provide needed ammonia metabolism and that the patient's life would not be threatened in the event of graft failure if the native liver were not removed. Because of the constraints imposed by space and hepatic vein outflow,^{14,15} an orthotopic position was chosen for the graft.

The left lobe of the recipient was removed and orthotopically a segment 2, 3 graft was placed as an auxiliary support. The left hepatic vein of the graft was anastomosed end-to-end to the recipient left hepatic vein. The portal venous supply was shared with the recipient's own remaining right lobe by end-to-end anastomosis with the recipient left portal vein. An arterial supply was obtained by an interposition graft to the recipient's infrarenal aorta.

Biliary drainage was accomplished with a Roux-en-Y jejunal loop.

Living-related Liver Transplants: Patient Selection and Donor Preparation

After a comprehensive analysis of the risks and benefits to donors and recipients and the ethical considerations of informed consent for potential donors,¹⁶ we began a clinical program of LRLT in November 1989. Five LRLT procedures were performed, all in infants with biliary atresia. These patients represent a preliminary group in an experimental protocol that is projected to include 20 patients. An elaborate process for informed consent is used to reduce coercion in the decision to donate, and recipients are medically stable infants with progressive liver disease. Following agreement of the family to proceed, a thorough medical and psychosocial evaluation is performed to determine the suitability of the donor. Eligibility for donation includes compatible blood group, acceptable size of the left lateral lobe, as determined by volumetric CT scan, and appropriate vasculature, as determined by celiac angiography. The five donors included two mothers, two fathers, and one grandmother, whose ages ranged from 20 to 42 years.

Donors were prepared for routine abdominal surgery. A bilateral subcostal incision was used, extended in the midline to the xiphoid. In the first three cases, hilar dissection was performed with isolation of the pedicle to the left lobe. The caudate lobe was separated from the vena

cava and the left hepatic vein was isolated. Following this dissection total hepatic ischemia was induced by clamping the hepatic pedicle and the vena cava. Under ischemia the entire left lobe was rapidly removed by transection in the principal scissure between right and left lobes; warm ischemia time for the graft was between 7 and 9 minutes. While the graft was being perfused with cold University of Wisconsin organ preservation solution containing heparin,¹⁷ hemostasis of the transected surface was completed in the donor. Hepatic ischemia ranged from 22 to 35 minutes in these three donors. In the last two cases, the technique was modified to reduce the extent of dissection in the donor and to avoid warm ischemia. The hilar dissection was performed to the left of the round ligament (Fig. 1), with isolation of the portal structures distal to the origin of the segment 4 pedicle. The left hepatic vein was encircled and controlled. Finally the parenchyma was transected to the left of the round ligament without ischemia, thereby leaving both segments 1 and 4 in the donor. After completion of the dissection, the vessels were divided and the graft removed and flushed. All lobes eventually were reduced to a graft consisting of segments 2 and 3. Vascular reconstructions were performed by using an inferior mesenteric vein graft obtained from the donor if needed.

Implantation of the graft was performed following recipient hepatectomy with preservation of the vena cava in all cases. The technique was identical to implantation of a segment 2 and 3 graft obtained from a split liver. The hepatic vein was anastomosed to the side of the vena cava and the recipient portal vein and common hepatic arteries were suitable for implantation in all cases. The hepatic artery and portal vein had to be extended in cases 1 and 5.

Results

Patient and Graft Survival

Patient survival and the frequency of retransplantation are summarized by graft type in Table 1. Overall the various modalities for using graft reduction have resulted in postoperative results similar to those achieved with full-size grafts, while pretransplantation mortality has been limited to less than 2%.

TABLE 1. Patient and Graft Survival by Graft Type in 106 Children (November 1986–February 1990)

First Graft	Alive*	Retransplantation
Full size	46/57 (81%)	24%
Reduced	18/23 (78%)	17%
Split	14/21 (67%)	35%
Live	5/5 (100%)	20%

* Follow-up as of April 1, 1990.

TABLE 2. Patient and Graft Survival in Patients Undergoing Split-liver Transplantation

Graft Type	Patient Survival	Graft Survival
Primary grafts (n = 25)		
Children	14/21 (67%)	12/21 (55%)
Adults	1/4 (25%)	1/4 (25%)
Retransplants (n = 5)		
Children	0/4	
Adults	0/1	

Split-liver Transplantation

Twenty-five SLT procedures were performed in 21 children (Table 2). Split-liver transplantation was associated with the highest failure rate and patient mortality among the procedures using reduced grafts (Table 1). Survival in children was 67% and 20% in adults. As we have described previously,¹² biliary complications have remained the principal difficulty in SLT in children, occurring in 27%. In five adults right lobe grafts from SLT were used exclusively in emergency situations. The diagnoses in adults selected for SLT included decompensated cirrhosis (n = 3), chronic graft failure (n = 1), and fulminant hepatitis (n = 1). Low-grade sepsis probably was present in four of these patients, and ultimately four of the five died of sepsis. Necrosis of segment 4 and bile leaks clearly contributed to the poor outcomes.

Auxiliary Liver Transplantation for Metabolic Disease

Auxiliary liver transplantation performed in a patient with a urea cycle defect (UCD) resulted in virtually immediate correction of the metabolic disturbance. Before transplantation the patient required a special diet (UCD formula) and could not tolerate more than 0.5 g protein per kilogram body weight per day. He also received medications that provided alternate pathways for ammonia excretion (Na benzoate, phenylacetate, and arginine). Despite this his ammonia level ranged from 80 to 1800 $\mu\text{g/dL}$ (nl < 85) and orotic acid was consistently detectable in the urine. As a result of the bouts of severe hyperammonemia, the patient suffered moderately severe central nervous system injury, which was not expected to improve after transplantation. The procedure was undertaken at the request of the parents to provide an opportunity for improved quality of life. The patient was able to receive a normal diet by 1 week after transplantation while receiving no medications. The blood ammonia was consistently normal and orotic acid was not detectable in the urine. He has maintained a normal diet with protein intake more than six times greater than before transplantation. He requires no medications or special diet for controlling ammonia. His body weight more than doubled in 6 months. Both the graft and the native liver take up

and excrete disphenen (HIDA). A biliary stricture localized to the anastomosis was identified 4 months after transplantation. At this time the blood ammonia increased, even though there was no other evidence of hepatic failure. The biliary obstruction was repaired without further complications. While the neurologic status of the patient has improved little, graft function has resulted in virtually normal metabolism of ammonia and a greatly improved quality of life.

Living Related Transplantation: Donor and Recipient Outcomes

Donor results of LRLT are summarized in Table 3. Complications occurred in the three donors who underwent total left hepatectomy for procurement of the graft. The first donor experienced two intraoperative complications, a retractor injury to the spleen and a 5-mm laceration in the anterior wall of the common bile duct. Splenectomy was required and the biliary laceration was repaired over a T tube, which was removed at 6 weeks after obtaining a normal cholangiogram. The second patient developed a subhepatic fluid collection, which was managed with percutaneous drainage and antibiotics. The third patient experienced a persistent biliary fistula, which has been managed with external biliary drainage. Patients 4 and 5, who underwent left lateral resections, have experienced no complications. Presently all five donors are at home with normal liver function between 2 and 6 months after operation.

Recipient operative courses and complications are presented in Table 4. The first patient developed a subcapsular hematoma of the extremely soft graft, which resulted in hemorrhage that required three operations to control. Subsequently there have been no further complications and liver function is normal after 6 months. The second and third patients have had no surgical complication, but patient 3 developed severe rejection, which required two courses of OKT3 to control. Both are at home with normal liver function 5 and 3 months after grafting. Recipient 4

TABLE 4. *Results of Living Related Liver Transplantation: Operative Data and Hospital Course in Five Recipients*

Patient	Time*	Blood†	Artery‡	Vein§	Complications
1	8.08	4/6/6	I	I	Subcapsular hematoma
2	6.5	3/3/0	E	E	—
3	7.5	3/5/0	E	E	Rejection (OKT3)
4	6.8	2.5/6/0	E	E	Bile-leak rejection (OKT3)
5	7.5	2/5/0	I	I	Bile-leak arterial thrombosis

* Anesthetic time (hours).

† Intraoperative transfusions: packed red cells/fresh frozen plasma/platelets.

‡ Hepatic artery: I, interposition; E, end-to-end anastomosis.

§ Portal vein: I, interposition; E, end-to-end anastomosis.

had two bile duct orifices to the segment 2 and 3 graft, but only one was identified at the time of transplantation. Two weeks later enzyme changes suggesting rejection resulted in biopsy, which demonstrated evidence of duct obstruction. This was confirmed by percutaneous cholangiogram, and at re-exploration she was found to have obstruction of the segment 2 bile duct. This was repaired over a silastic stent with a good technical result. This patient also has experienced steroid-resistant rejection, which has responded to OKT3. Presently, 2 months after transplant, there is some cholestasis but otherwise normal liver function. The fifth patient developed acute biliary dilatation and infarction of segment 3 two weeks after transplant. This was initially managed with resection of segment 3, but it became clear that the entire arterial system of the graft was occluded. Retransplantation was performed with a segment 2, 3, and 4 graft obtained from a cadaver donor, and the patient has normal liver function 2 weeks after retransplantation. The grafts obtained from LRLT have, in general, been extremely soft and readily perfused at implantation. Early function has been good with rapid normalization of the prothrombin time.

Complications of Reduced Grafts

Complications by graft type are summarized in Table 5, whether the grafts were used as primary grafts or retransplants. Most of the complications occurred in SLT. Complications occurred with similar frequency, regardless of the lobe used. Several observations are of interest. First hepatic vein obstruction is a syndrome unique to left and left lateral lobe grafts in which the recipient's vena cava is used. All four cases of hepatic vein obstruction occurred when the recipient left hepatic vein was used with creation of an end-to-end anastomosis. Second arterial thrombosis has occurred at an incidence lower than that experienced for full-size grafting in our series. Arterial thrombosis was identified in four patients with reduced grafts, three of

TABLE 3. *Results of Living Related Liver Transplantation: Operative Data and Hospital Course in Five Donors*

Age (years)	Sex	Time*	RBC†	Complication	Days‡
29	F	7	4	Splenectomy	8
20	M	5.7	2	Subhepatic collection	7
27	F	8	0	Bile leak	12
42	F	7.1	0	None	6
35	M	6.5	0	None	7

* Total anesthetic time (hours).

† Intraoperative red cell units transfused.

‡ Postoperative days prior to discharge.

TABLE 5. *Summary of Surgical Complications of Graft Reduction in Adults and Children (n = 61)*

	Graft Type (Segments)*				Total
	2, 3	1, 3, 4	5-8	4-8	
Number of grafts	19	25	13	4	61 (100%)
Hemoperitoneum	6	4	2	1	13 (22%)
Biliary leak/ obstruction	2	4	3	2	11 (19%)
Arterial thrombosis	1	0	2	1	4 (7%)
Graft nonfunction	3	2	0	0	5 (8%)
Partial necrosis	1	0	1	2	4 (7%)
Portal vein thrombosis	3	2	0	0	5 (8%)
Hepatic vein obstruction	2	2	0	0	4 (7%)

* Hepatic segments according to Couinaud (Fig. 1).

whom developed partial graft necrosis. These three included one infant who received a left lobe SLT, another infant recipient of a LRLT, and an adult recipient of a right lobe plus segment 4 of a SLT. Third partial hepatic necrosis occurred in two of four adult patients in whom segment 4 was preserved with the right lobe graft in SLT; outcome was poor in these cases.

Discussion

Pediatric patients who are potential candidates for OLT have a significant risk for dying before a donor becomes available.^{18,19} This combines with postoperative mortality to create a global mortality rate for this population that is probably greater than for adults, despite the fact that pediatric survival is reported to be better than for adults in most series of OLT. The shortage of donors for small children and the consequent long waiting times and high mortality rates among pediatric candidates for OLT have driven our program of innovative surgery. The principal accomplishment of the program is a pretransplantation mortality rate of less than 2%. This, if not countered by an inordinate increase in post-transplantation mortality, would effectively reduce the global mortality of end-stage pediatric liver disease by as much as 25%. An equipoise analysis of the use of RLT demonstrated that a 50% postoperative mortality rate would be acceptable and not increase overall mortality.²⁰ Any survival greater than that would result in gain when global mortality is considered. The results presented here indicate that survival after liver transplantation with a RLT, no matter what the source, is as good as whole-liver transplantation. Therefore the reduction in the pretransplantation mortality rate is translated directly into an improved overall survival rate.

These gains have been accomplished at some cost however. The procedures using lobes for grafts are more complex than whole-liver transplantation and are associated

with more postoperative complications. However there is no truly comparable group of patients against which to measure the results of RLTs because their use has allowed for more small infants to be treated with OLT than could be accomplished with whole-liver transplant. Therefore the patients reported here have a rate of complications that might be unacceptable for recipients of whole-liver transplants, but they were smaller and more sick than any reported series of pediatric recipients. One half of the recipients in our program weight less than 12 kg and two thirds weight less than 20 kg. Therefore the increased morbidity realized in this series is the result of several factors, some of which may not be the direct result of the surgical procedures.

Split-liver transplantation represents a special case of reduced-size grafting because of its complexity. Split liver transplantation was associated with numerically higher morbidity and mortality rates, but it must be remembered that in virtually every instance at least one of the recipients was in emergency status. We now use SLT whenever possible, but for most of this series it was used when one patient, usually the larger and recipient of the right lobe, needed emergency therapy. A smaller recipient was selected from the waiting list by need and blood type. We performed no truly elective transplants using SLT. More recently we have performed SLT in some cases in which the donor was identified for a larger recipient waiting for transplantation but not in an emergency. In effect we now split every donor liver to be used in a pediatric patient, if possible. We are reluctant to remove the left lobe of livers destined for adult recipients because of the poor results when this is done. We do not place an adult recipient at increased risk to benefit a child. Furthermore we do not split livers that are the appropriate size for the primary recipient who is a child, but only when a graft reduction will be needed. Finally we do not split very small livers (*i.e.*, those from donors who weigh less than 10 kg) because of the size of the lobar hepatic artery.

Two complications occurred with greater frequency in the experience with SLT and are the result of the procedure. One, necrosis of segment 4 when it was left with the right lobe to increase the graft mass for the larger recipient, is completely avoidable. Segment 4 should be discarded if not given to the smaller recipient as a left lobe (segment 2,3 and 4) graft. Its vascular and biliary integrity cannot be assured otherwise. The other complications that occur with greater frequency in SLT relate to the bile duct of the left lateral segment grafts. The left bile duct system trifurcates at the round ligament. If the parenchymal transection is to the left of this structure when segment 4 is removed (Fig. 1), two or more bile duct orifices must be identified and drained. If one or more is not identified, obstruction of part of the biliary system results. Elevated

cholestatic enzymes (*i.e.*, alkaline phosphatase and γ -glutamyl transpeptidase) and ductular proliferation in portal areas of tissue obtained from the affected segment herald the problem. However bile duct obstruction can be difficult to diagnose because cholestasis may not be evident and these tiny bile ducts do not always dilate enough to be identified by ultrasound. Biliary infection and segmental biliary cirrhosis lead to graft dysfunction, which necessitated retransplantation in two of our patients. We try to solve this by preserving the main left hepatic duct and its surrounding vascular structures, and using it to drain the segment 2 and 3 graft. If this is not possible, careful identification and separate anastomosis of the ducts of segment 2 and 3 have allowed successful transplantation. If these complications can be overcome, SLT is a very useful approach because it provides two grafts, one of which can be used in a patient who is healthier who thus benefits from the procedure for the patient who is in an emergency situation.

Our single case experience with ALT provides the feasibility data for using auxiliary grafts for the treatment of metabolic disease. Inborn errors of metabolism often involve primarily hepatic metabolic pathways while their effects are systemic. Few of them cause destruction of the liver itself. Most of these metabolic pathways are normally present in large excess, and as a consequence, in theory only a small portion of liver is required for their correction. The approach to date has been to replace the entire liver, even though this is not necessary. Based on the experience by Terpstra et al.²¹ using hepatic lobes as heterotopic auxiliary grafts in patients with cirrhosis, we think a similar approach is warranted in treating a child with urea cycle defect (OTC deficiency). We placed the graft in the orthotopic position for several reasons. First, contrary to the European experience, we wanted both the native liver and the graft to survive indefinitely. The graft had to provide urea synthesis, while the native liver would provide protection from liver failure should the graft fail as a result of rejection or other complication. Second the infant's abdomen would not easily accept the additional mass of an auxiliary graft. Finally a position near the diaphragm would assure proper hepatic venous outflow. The main concern was to assure adequate portal blood flow to the graft in a system in which flow to the right lobe was not impeded by hepatic fibrosis. The outcome in this case demonstrates the feasibility of the procedure.

Auxiliary liver transplantation could be used to treat many disorders characterized by defective metabolism without anatomic liver disease (*i.e.*, cirrhosis). The urea cycle defects,²² disorders of fatty acid metabolism (such as medium chain acyl-CoA decarboxylase deficiency), and other disorders of intermediary metabolism could all be managed this way, at least in theory. Early intervention

could prevent the development of irreversible central nervous system injury, such as our patient suffered. Other disorders that could benefit from ALT include disorders of hepatic synthesis. Hemophilia, for example, could be treated in this way; the cost of the procedure is small when contrasted against the cost of life-long use of human clotting factors, and the risk may not be greater. Severe familial nonhemolytic jaundice (Crigler-Najjar syndrome)^{23,24} and familial hypercholesterolemia,²⁵ which is a deficiency of hepatic LDL receptors, both have been treated with OLT but could be approached with ALT with reduced patient risk. This procedure may become the treatment of choice for these and many other diseases of metabolism.

The most recent innovation reported here is LRLT. The ethical considerations considered before the advent of the clinical program have been discussed in detail elsewhere. This medical/surgical innovation is a natural evolution of SLT. The donor, usually a parent, after a complete medical evaluation that includes determination of the size and anatomy of the left lateral lobe, undergoes partial hepatectomy. A left lateral lobe graft is prepared, which is used just as it is in split-liver transplantation. The obvious advantages to this technique are a donor for essentially every recipient, an improved quality as a result of a transplant from a healthy living donor, and perhaps improved histocompatibility. The preliminary results in five patients treated suggest it will be a useful addition in pediatric transplantation, although there have been some problems.

Donor morbidity has been significant. Complications can be classified into inadvertent and perhaps unpreventable accidents and those that presumably can be eliminated with increased experience. The rupture of the spleen in donor 1 is the only serious accident encountered in our series. The same patient's bile duct was lacerated during the rapid removal of the graft under warm ischemia. These problems were overcome with no apparent morbidity. The bile leak in donor 3 has been more of a nuisance than a risk to the patient. We think they can be prevented in future cases by limiting the resection to segments 2 and 3 or by meticulous parenchymal transection before vascular clamping. Limiting the resection to segments 2 and 3 is preferable because of the ease of the donor operation. However we think this may be balanced against more problems in the recipient related to the bile ducts, as described above.

The five recipients of LRLD have experienced few complications. Recipient 1 had a hematoma with subsequent hemorrhage from the anterior surface of the graft related to a contusion suffered in the donor at the time of splenic rupture. Patient 4 had an obstruction of the segment 2 bile duct, which was corrected. Patient 5 ex-

perienced thrombosis of the hepatic artery 2 weeks after transplantation and after the patient had been discharged from the hospital. Two patients have had severe steroid-resistant rejection that was managed by administration of OKT3. All patients are alive and well, with only patient 5 requiring retransplantation.

The positive aspects of LRLT that have been realized relate to the initial graft function. These grafts have been very soft and easily perfused. The initial function has been outstanding and has been maintained despite patient complications at a level not usually seen in cadaver grafts. Finally the patients have had excellent short-term courses with the LRLT graft, except for recipient 5. These early results encourage us to complete the protocol that involves LRLD in 20 infants.

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DISCUSSION

DR. JOHN S. NAJARIAN (Minneapolis, Minnesota): I would like to mention that Dr. Henri Bismuth, inducted this year as an Honorary Fellow of this Association, did point the way to introducing the methods for using reduced-size livers as well as split livers. However, we are all also indebted to Dr. Broelsch, who used these techniques extensively. Two years ago he presented to this Association a large series of his own on the use of reduced-size livers for children with end-stage liver disease.

What this has done for those of us interested in liver transplantation in children is to reduce the number on the waiting list at our own institutions.

The number of children at our hospital who were waiting for liver transplants was increasing, but because of the success reported by Bismuth and Broelsch, we began using reduced-size adult livers and we have been very pleased with this important technical advance in liver transplantation in children. So from that point of view, I am very pleased.

In Dr. Broelsch's series, using reduced-size livers has also reduced his own waiting list. Only 2% of his patients currently are dying while waiting

for a liver transplant. Thus, he obviously has reduced his own waiting list rather remarkably just with the reduced-size livers and with split liver donors.

The problem I have relates to split livers where you use two halves of an adult liver for two recipient children. As we saw, the results aren't nearly as good as with reduced-size livers and whole organs. Patient survival is around 67%. Grafts that do survive are functioning in 50% of the children. That breaks down to graft survival of 64% for children and 20% for adults.

So, therefore, my first question, Dr. Broelsch, is why are the split liver results so bad? Is it the "emergent" case that is dragging the results down? If so, when you break it down by "emergent" versus elective cases, are your results better with the elective cases than with both kinds combined?

I am very intrigued by your auxiliary transplant. It is such a beautiful model for providing endocrine support to someone who is endocrine deficient or enzyme deficient. I am anxious to hear more about that group because we have been doing something similar with orthotopic liver transplants, and are considering them for patients with oxalosis. We are very interested in the results you have achieved and in the future

plans you have for using the left lateral lobe added on to the patient's own native liver. My only concern is if the segment does reject, you are right back where you started. Will you have really gained a lot?

I am a strong and vocal advocate of living related donors, as Tom Starzl has pointed out and as I have stated at many national meetings. Having used over 2000 living related kidney donors and some 75 living related pancreas donors, I would be very supportive of using livers from living related donors. However, I have some major concerns about this procedure and I would like to play the devil's advocate and examine your published ethical analysis. You have stated three important points, and I would like to discuss each one.

First, the *need for the procedure*. If, in fact, you have reduced your waiting list to the point of only losing 2% of those children waiting for a liver transplant, is there a need to use a living related donor?

Second, the *benefit from the procedure*. As I look at it, the procedure is basically the split liver transplant. If it is, and since the split transplant results aren't good, isn't the benefit less than it would be with a reduced-size cadaver liver or with a cadaver infant liver?

Third, the issue of *informed consent*. This is a problem we run into often when looking at parents as donors of kidneys for their children. Is it possible to really get informed consent from a mother or father or grandmother who is emotionally very involved, and is told that the child is dying but can be saved if they act as the donor? No matter how you explain that, they are going to say yes. If they say no, the eventual guilt could be fantastic.

I really applaud you, though, on looking at those ethical and legal questions and publishing them in the *New England Journal of Medicine* and the *Journal of the American Medical Association*. You have done the groundwork very well, and for that, should be congratulated.

Finally, I have always had a problem with retransplantation. We have transplanted livers in 112 children, and retransplanted nine of them—a total of 8%. The retransplantation figures you have presented are 24% for full-size livers, 17% for reduced-size livers, and 35% for split livers. Wouldn't the best thing for the present organ shortage be to avoid such a high level of retransplantation? I am sure you are looking at that. I know the Pittsburgh group also reports a high rate of retransplantation. We have always thought that as long as we are very selective in the organs we obtain, we can maintain a low retransplantation rate and not deplete an already short supply of these precious life-saving donor organs.

I congratulate you on a fantastic series and a beautiful clinical experience with reduced-sized livers and split livers. This experience has stimulated many of us to transplant more children than we were doing before.

DR. R. PETER ALTMAN (New York, New York): I am pleased to comment on this innovative work from a pediatric surgeon's perspective. This paper has particular relevance to those of us who take care of infants with biliary atresia awaiting transplantation.

Our experience in New York with 130 patients indicates that about one third will live jaundice-free and perhaps be cured by Kasai's operation. Another third of the patients will be palliated and have extended survival.

Dr. Broelsch's work is important for the absolutely miserable group of infants that are neither cured nor palliated. Some will have accelerated liver failure and die without whole liver, reduced liver or split liver transplantation.

Despite nutritional support, these infants do not grow. They bleed from varices and require endoscopic therapy and are admitted repeatedly for diuretic management, notwithstanding the expenditure of financial and emotional resources, many die waiting for transplants.

Through the efforts in Chicago with reduced-size and now split liver grafts, the donor pool has expanded and undoubtedly many infants are rescued.

Furthermore children weighing less than 10 kg are transplanted. These might otherwise have been excluded because of technical considerations.

Acknowledging the excellent results achieved with split livers, the results are not equivalent to those achieved with whole organ or reduced organ transplants.

I have two questions for Dr. Broelsch. Might dividing a high-quality organ compromise the outcome for one or even both recipients? What are exactly are your criteria for deciding to split an organ and share it in two recipients?

DR. HENRI BISMUTH (Villejuif, France): When I opened the field of 'partial grafting' more than 10 years ago using a reduced-sized graft for a heterotopic transplantation in an adult patient with end-stage liver failure, it was only to obtain smaller graft to fit into the patients abdomen below his own liver.

I would like to ask Dr. Broelsch two questions. The first is, do you try to determine before surgery in the living donor, the intrahepatic distribution of the bile ducts within the left lobe, and if you do so, how do you do it?

My second question is about your fascinating case of auxiliary transplantation, replacing the left lobe of the patient by the left lobe of the donor. One of the difficulties of this operation is the portal perfusion of the graft. I experienced this difficulty, about 7 years ago, when I performed the same operation in an end-stage patient, replacing the diseased left lobe of his cirrhotic liver by the normal lobe of a donor. This patient had had a side-to-side portacaval shunt previously, and when I attempted to close this, the small graft became tense. I thought this was due to a hyperdynamic flow within the graft, in relation to the high portal vascular resistance of the patient's liver on the right. Therefore, I left the shunt partially open to decompress the graft. Retrospectively, I think this was indeed a mistake, for during the following week the graft did not work well.

In the case Christopher Broelsch reports here, the hemodynamics of the liver of his patient are normal.

You said that you shared the portal blood between the two livers, but in the case of an increased portal resistance due, for instance, say, to a rejection episode, the portal flow may be completely diverted through the patient's own normal liver, depriving the graft of portal flow.

Did you modify the portal vein of the recipient in order to give some preference to the graft, knowing, however, that this can be disadvantageous to the remaining liver of the patient?

The competition between the two livers in auxiliary transplantation seems to be difficult to overcome when the patient's liver has only metabolic disease and is apparently normal.

Above all, I would like to congratulate Dr. Broelsch for his pioneering work in the living donor. Many groups are waiting throughout the world to follow him, and this will be an enormous step forward in liver transplantation.

DR. JEREMIAH G. TURCOTTE (Ann Arbor, Michigan): I want to point out something that has not been emphasized either in the media or in the scientific literature. Most of the world does not have so-called brain-dead cadaver donors available. If Dr. Broelsch's experiment works out with good results for the recipient and is of low risk to the donor, this will open up liver transplantation to the great majority of the world in which it is not now available.

DR. CHRISTOPH E. BROELSCH (Closing discussion): I would like to focus on a few questions—to Dr. Najarian's question: Why are the initial results so bad?

First, indeed, we are somewhat disappointed with that, too, but I think we have a couple of explanations.

When we presented our first series of reduced size, you might remember that we had a similar bad experience in the beginning. Most of the reasons were really technical. For the present series, I alluded to three cases where we had problems with the perfusion of the median left lobe (segment 4), which we now resect mandatorily. Perfusion damage resulted in total ischemia of the lobe and development of sepsis, whereas infections from the cut margin have not otherwise occurred.

Secondly, we have learned our lesson in terms of detecting bile duct problems and identifying bile duct abnormalities. Both had been a problem in the beginning. We have obviously obstructed several small bile ducts in the beginning, not realizing that occasionally there are up to three small bile ducts draining the left lateral segment that join to a confluence in the media left lobe. Those were not identified by us at the time of transplantation, and we have ligated one and have obstructed another. This has not become a problem in the recent series, and I think those technical considerations explain part of the initial failures.

To answer jointly one of Dr. Bismuth's questions, too: We occasionally, not routinely, take intraoperative ultrasound for anatomic orientation;

but we are primarily looking at portal venous abnormalities and other biliary abnormalities in the hilum, because apparently there are anatomic variations as to which branches of the portal vein drain into the left median segment and which artery supplies the left lobe.

Before the living donor hepatectomy, we always obtain an angiographic identification so we know where the hepatic artery is located and where it branches off. In addition we look at the intrahepatic portion of the portal vein to find out about the lobar circulation.

However, in cases where we resect the left lateral segment only—which is a substantial reduction of the trauma to these donors—we look very carefully at the drainage of the median left hepatic vein and try to preserve it. Even in those anatomic abnormalities with crossover venous drainage, I would say that the left lateral lobectomy can be performed safely.

The price we pay for the minimizing of the donor's trauma is that we have to reconstruct the hepatic artery and often the portal vein as well, because they are not sufficient in length to reach the portal structures of the recipient. However, when we take the entire left lobe out, we have more length on the vessels. During a bench procedure, the median left lobe is removed and we obtain additional length of hepatic artery and portal vein, and no reconstruction is needed. However the reconstructions only led to complication in one case. Of course one case in this small series accounts for a large 'percentage.'

Dr. Najarian mentioned 20% survival in the series of five (adults), and I honestly report these. All five patients were adults, retransplant cases ($n = 3$), or acute liver ($n = 2$) failure. Patients would not have qualified sometimes for primary transplants. So whenever we had one liver available but had several patients to transplant, we decided (to not waste a liver) to give it to one of the adults and simultaneously split the transplant to benefit another pediatric recipient.

We believe that this splitting of cadaveric organ will make a difference in organ availability in the future, and the results accomplished to date are indeed better.

The liver donor problem was addressed, too, and represents a variety of problems. Let me focus on the informed consent, the voluntarism of the donor, and the need of the procedure.

If we could provide organs for all children from cadavers by splitting them, is there a need for any living related organ donation? I believe yes; because with the growing number of candidates, I still see a need for the living related procedure because we cannot simply meet the demand for cadaveric organs, particularly when time constraints exist. However we do not want to make those procedures interchangeable. The living related procedure is a totally elective procedure, and the information to the parents is: you can do this living donation, but we have a menu of transplantations at our institution, including a reduced-size, split, or full-size transplantation, if you want to wait. We are prepared to do either one.

This, I think, takes away the argument of a potential coercion we want to eliminate on those patients when we present the option of the living related transplantation. Parents are willing, and this might surprise you, to even take on a 15% to 20% mortality risk to benefit their children. It shows how the whole response can be irrational and emotional; and therefore, we try to put a rationale on the information process by explaining all the potential complications and the alternatives of the treatment. If the answer is positive, I think that in elective circumstances, not as a general rule yet for transplantation, the living related will have a place and more parents will volunteer. Probably in the future, adults with acute liver failure might want to have this procedure done which, would require special addenda to our existing protocol.

To Dr. Altman's question, the criteria you alluded to for sharing of split organs are clearly not established at this point. Sharing could mean that we bring an organ to another institution. At present, we are only sharing in our own institution where we have two potential recipients at the same time in our hospital, so we can make a decision once the organ has returned to our institution as to which recipient would have the appropriate size and would have the appropriate anatomy to receive this organ. In the future, if organ shortage becomes a more pressing issue, sharing between institutions might have to be developed. We did this actually with one of our first cases who represents one of the adults where we shipped the right lobe to an unstable critical patient at the St. Louis University for transplantation. Unfortunately, the patient died on the operating table for other reasons; but this incidence is included in our series.

Reoperation for Coronary Atherosclerosis

Changing Practice in 2509 Consecutive Patients

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We analyzed trends in clinical, angiographic, and operative variables and documented long-term survival in 2509 consecutive patients who underwent reoperation for myocardial revascularization at The Cleveland Clinic during a 20-year period (1967 to 1987). The patients were grouped into four cohorts by year of surgery. This analysis showed that vein graft atherosclerosis has become the leading indication for reoperation, and patient age and interval between operations continue to increase. Mortality rates ranged from 2% to 5% and, despite increasing comorbidity, more extensive coronary atherosclerosis, and worse left ventricular function, the hospital mortality rate was 2.9% from 1985 to 1987. Perioperative new Q-wave myocardial infarction occurred in 7% to 8% of patients from 1967 to 1984 but decreased to 4% in the 1985 to 1987 period ($p = 0.04$). Internal thoracic artery graft usage in reoperations increased from 27% in the 1967 to 1978 period to 67% in the 1985 to 1987 period. Advanced age and presence of left main coronary artery disease adversely influenced late survival more consistently than other factors. Patients operated on in 1967 to 1978 had fewer risk factors, which explains their higher survival rate compared with more recent cohorts. Factors associated with improved 10-year actuarial survival included age younger than 65 years, mild angina, no major comorbidity, no left main coronary artery disease, good left ventricular performance, and an internal thoracic artery graft.

IN THIS THIRD decade of direct myocardial revascularization, three determinants of outcome are acknowledged: the patient, the operation, and progression of coronary atherosclerosis. We know that the characteristics of the patient and the operation are changing.¹⁻³ As operative practices change, outcome analyses are necessary to base selection of therapy on documented efficacy. In coronary bypass surgery, primary end points are survival rates and late cardiovascular events. A coronary artery reoperation is one of these events.

We report (1) changing characteristics of patients undergoing coronary artery reoperations, (2) trends in early reoperation results, and (3) determinants of long-term survival and late cardiac events. This series of 2509 patients updates a report on coronary artery reoperation⁴

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by adding 1009 more consecutive patients who had a second operation from 1985 through 1987. This consecutive series of isolated reoperative coronary artery surgeries performed in one institution spans 20 years.

Methods

Consecutive isolated coronary artery reoperation patients were identified; data on these 2509 patients were obtained from a computerized Cardiovascular Information Registry. All individual patient records were cross-checked with original computer entries and any discrepancies were resolved by the authors and recoded in the database. Patients with three or more coronary artery operations were excluded. The clinical, angiographic, and operative descriptions were defined previously.⁵ Actuarial survival curves were computed according to the Kaplan-Meier method. Univariate comparisons for survival curves were calculated by the Wilcoxon test and all multivariate analyses were performed with Cox proportional hazard models.

The patients were grouped by the year of reoperation into four cohorts: 1967 to 1978, 436 patients; 1979 to 1981, 439 patients; 1982 to 1984, 625 patients; and 1985 to 1987, 1009 patients. Mean patient age at first and second isolated coronary operation and interval between operations were determined (Table 1). The interval between operations changed from a mean of 50 months in the first cohort to 101 months in the most recent cohort ($p = 0.0001$). The prevalence of reoperation in women increased through 1984 and then declined.

Angina was classified by New York Heart Association (NYHA) functional class I-IV. Diabetes, hypertension, and peripheral vascular disease were noted more frequently in the most recent group (1985 to 1987) compared with the earliest group (1967 to 1978) (Table 2). Severe coronary atherosclerosis was defined as a lesion that narrowed the arterial lumen by an estimated 50% or more.

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TABLE 1. Cohort Size, Gender, Mean Ages, and Interval Between Operations in 2509 Reoperation Patients

Demographics	1967-1978 (n = 436)	1979-1981 (n = 439)	1982-1984 (n = 625)	1985-1987 (n = 1009)
Sex	38 (8.7%)	58 (13.2%)	91 (14.6%)	117 (11.6%)
Female	398 (91.3%)	381 (86.8%)	534 (85.4%)	892 (88.4%)
Male				
Mean age at first operation (years)	49.1	50.3	51.2	52.5
Mean age at second operation (years)	52.3	56.3	58.2	60.9
Interval between operations (months)	50	72	84	101

The incidence of left main coronary artery narrowing increased from 51 cases (12%) in the first cohort to 253 (25%) in the most recent cohort ($p < 0.001$). Three-vessel disease, excluding patients with left main narrowing, increased significantly from 222 (51%) to 623 (62%) ($p < 0.001$) throughout the experience. Thus one- and two-vessel disease accounted for a decreasing percentage of patients over time.

Left ventricular performance, estimated subjectively, worsened in each succeeding cohort. In the earliest experience, normal left ventricular contraction was found in 263 (60%), but declined to 366 (36%) in the most recent experience ($p < 0.001$). In the latest cohort poor left ventricular function was found in 104 (10%) of patients. When left ventricular contraction before the first operation was compared to contraction before reoperation, 135 patients (31%) in the 1967 to 1978 cohort; 140 patients (31.9%) in the 1979 to 1981 cohort; 199 patients (31.6%) in the 1982 to 1984 cohort; and 219 patients (21.6%) in the 1985 to 1987 cohort lost previously normal left ventricular function in the interval between the two operations.

As in our previous reports on reoperations, patients were also grouped by angiographic indications for coronary artery reoperation. In addition to severe coronary arterial narrowing, the principal angiographic indications

were graft closure, progressive atherosclerosis in coronary arteries (either previously grafted or ungrafted), or a combination of graft closure and progressive atherosclerosis (Table 3). Graft closure, either alone or combined with progressive atherosclerosis, increased from 197 cases (45%) in the first cohort to 854 (85%) in the last cohort ($p < 0.001$).

Early Results

The 1985 to 1987 cohort received significantly more grafts per patient and more complete revascularization than the 1967 to 1978 cohort. Internal thoracic artery grafts increased from 27% in the 1967 to 1978 cohort to 67% in the 1985 to 1987 group. Of 1313 patients (52.3%) who had internal thoracic artery grafts, 112 (8.5%) occurred in patients with previous internal thoracic artery grafting and 1201 (91.5%) occurred in patients without previous internal thoracic artery grafting. The number of grafts per patient increased from 1.5 to 2.8 throughout the four cohorts. Similarly complete revascularization increased from 222 (51%) to 779 (77%). The mortality and major morbidity rates, grouped by patient cohort, are shown in Table 4. The operative mortality rate ranged from 2% to 5% and was 2.9% in the last cohort. Hospital death was attributed mainly to ischemia/infarction, which accounted for 38 (74.5%) of 51 early deaths in the first three cohorts, compared with 18 (67%) of 27 deaths in the most recent cohort (not significant [NS]).

New Q-wave perioperative myocardial infarctions changed from 7% to 8% in the first three cohorts to 4% in the last cohort ($p = 0.007$). Return to the operating room for bleeding and blood transfusions occurred significantly less in the 1985 to 1987 experience compared with the 1967 to 1978 cohort. Neurologic, respiratory, and wound problems did not vary significantly with time.

A logistic regression analysis was used to determine operative risk factors. Twenty-three clinical angiographic or operative variables (listed in the Appendix) were tested by univariate analysis and 11 were significant at the $p < 0.05$ level. These risk factors were entered into a logistic

TABLE 2. Incidence of Significant Comorbidity and Other Risk Factors in Reoperation Patients

Clinical Characteristics	1967-1978		1979-1981		1982-1984		1985-1987		p value*
	n	(%)	n	(%)	n	(%)	n	(%)	
Severe angina (NYHA III or IV)	319	(73.2)	312	(71.2)	419	(67.0)	647	(64.0)	0.001
Diabetes	62	(14.2)	67	(15.3)	107	(17.2)	230	(22.8)	<0.001
Hypertension	117	(26.8)	143	(32.6)	205	(32.8)	353	(35.0)	0.002
Peripheral vascular disease	29	(6.7)	52	(11.8)	76	(12.2)	140	(13.8)	<0.001
Obesity	61	(14.0)	76	(17.3)	113	(18.1)	182	(18.1)	0.06
Cigarette smoking	123	(28.1)	94	(21.4)	133	(21.3)	237	(23.5)	0.06

* p value reflects difference between 1967-1978 and 1985-1987 cohorts.
NYHA, New York Heart Association.

TABLE 3. *Angiographic Indications for Reoperation and Corresponding Intervals Between Procedures*

Procedure	1967-1978		1979-1981		1982-1984		1985-1987	
	n	(%)	n	(%)	n	(%)	n	(%)
Graft closure	123	(28.2)	157	(35.8)	278	(44.5)	254	(25.2)
Mean interval (months)		25.6		48.3		66.2		83.1
Progressive atherosclerosis	239	(54.8)	121	(27.6)	112	(17.9)	155	(15.4)
Mean interval (months)		63.2		93.5		111.2		113.3
Combination of above	74	(17.0)	161	(36.7)	235	(37.6)	600	(59.5)
Mean interval (months)		45.4		79.6		91.2		105.6

regression model and operative risk factors were determined: age ≥ 60 years, blood transfusion, three-vessel disease, left main coronary artery disease, current cigarette smoking, no internal thoracic artery graft at first operation, severe angina before reoperation (functional classes III and IV), interval greater than 60 months between operations, poor left ventricular function, and surgery during the period 1967 to 1978 (Appendix). Significance, relative risk, and confidence intervals were calculated.

Major complications in reoperation patients were compared with the first 1000 primary isolated coronary artery bypass patients, who were operated on from 1967 through 1987. These patients were grouped into cohorts corresponding to the patients in this reoperation series. Primary ($n = 16,996$) versus reoperation ($n = 2509$) incidences are as follows: mortality, 1.1% versus 3.2%; perioperative myocardial infarction, 2.1% versus 5.9%; return for bleeding, 4.8% versus 6.2%; respiratory complications, 2.0% versus 3.9%; stroke, 1.6% versus 1.8%; and wound complication, 1.6% versus 1.6%. Excluding stroke and wound complication, these differences were highly significant. Raw numbers are available in the Appendix. Median length of hospitalization and postoperative hospitalization period in days and by cohort were 1967 to 1978, 14 and 10; 1979 to 1981, 13 and 9; 1982 to 1984, 11 and 8; and 1985 to 1987, 11 and 8.

Late Results

The 2429 hospital survivors were followed for a mean of 72 months. The 1967 to 1978 group was followed for

a mean of 140 months; the 1979 to 1981 group was followed for 96 months; the 1982 to 1984 cohort was followed for 70 months; and the 1985 to 1987 cohort was followed for 34 months. Incomplete follow-up occurred for 28 (1.1%) of patients, 17 from the first 1500 patients and 11 from the last 1009.

After an overall mean follow-up of 72 months, 1888 living patients were classified according to NYHA functional class as follows: class I, 1199 patients (64%); class II, 506 patients (27%); class III, 153 patients (8%); and class IV, 30 patients (2%). Fifty-six survivors were not classified at follow-up. We found that those who had mild angina, class I or II before reoperation, tended to remain class I or II more than did those who had severe angina before reoperation; this observation held true in all four cohorts. Of patients who were in classes I and II before reoperation, 619 (93%) were in classes I and II after reoperation and 44 (6%) were classed as III or IV. In contrast, of 1223 who were in classes III and IV before reoperation, 1086 (89%) were classed I or II after reoperation and 139 (11%) were III or IV ($p < 0.0001$).

Eight hundred ninety postoperative coronary arteriograms were performed in 684 patients; only the last arteriogram after reoperation was reviewed. The mean interval between reoperation and the postoperative coronary arteriogram was 58 months (SD = 44 months). Of 411 internal thoracic artery (ITA) grafts studied, 363 (88%) were patent and 932 (65%) of 1438 saphenous vein grafts were patent. Patency for anterior descending and diagonal grafts was as follows: ITA, 308 of 346 grafts (89%); and

TABLE 4. *Mortality and Major Morbidity in Reoperation Patients*

Mortality and Morbidity	1967-1978		1979-1981		1982-1984		1985-1987		p value
	n	(%)	n	(%)	n	(%)	n	(%)	
Operative mortality	20	(4.6)	10	(2.3)	21	(3.4)	29	(2.9)	NS
Perioperative myocardial infarction	29	(6.7)	29	(6.6)	50	(8.0)	41	(4.0)	.007
Return for bleeding	48	(11.0)	28	(6.4)	26	(4.2)	54	(5.3)	<.001
Blood transfusion (units)	8.0		2.5		2.0		2.7		<.0001
Neurologic deficit	8	(1.8)	8	(1.8)	16	(2.6)	14	(1.4)	NS
Respiratory dysfunction	25	(4.0)	6	(1.4)	34	(5.4)	42	(4.1)	NS
Wound complication	9	(2.1)	6	(1.4)	9	(1.4)	17	(1.7)	NS

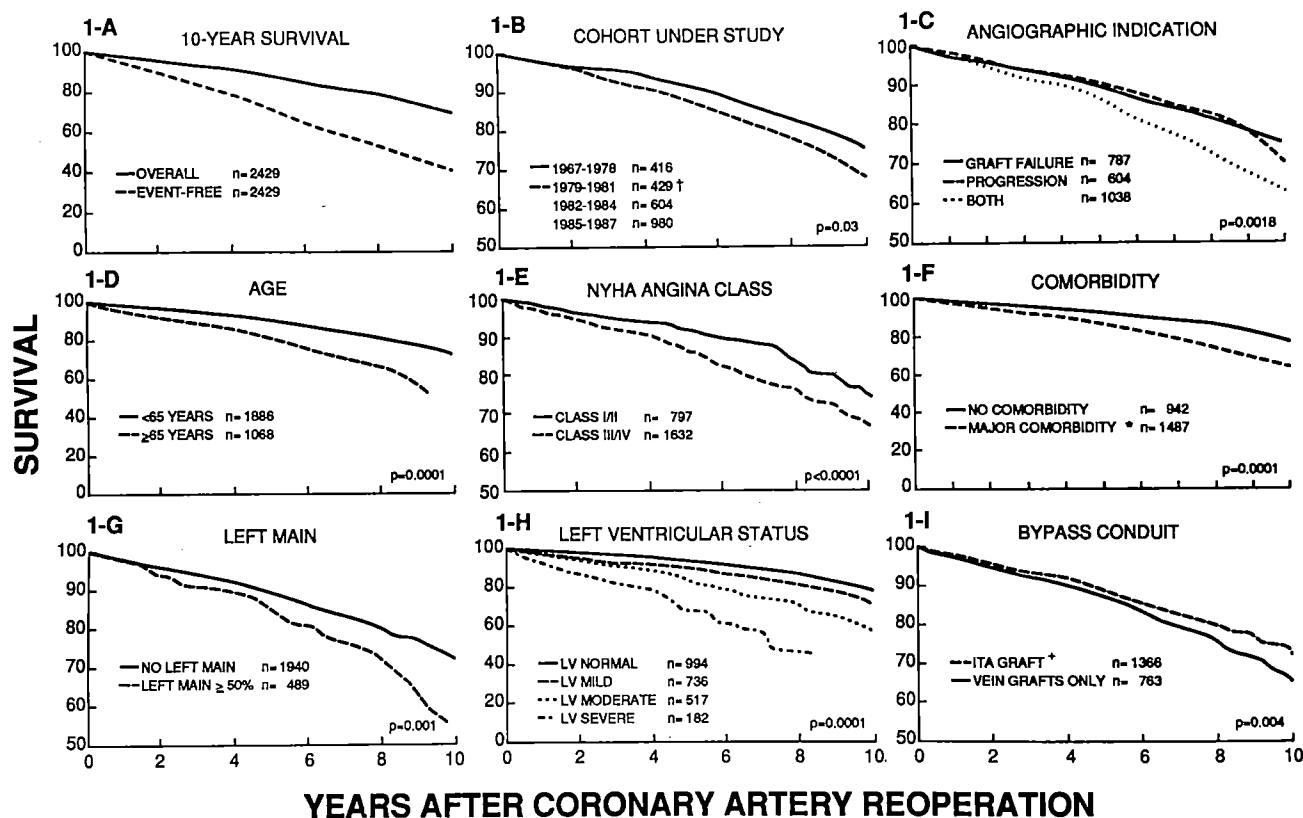
NS, not significant.

vein grafts, 342 of 481 grafts (71%); compared with patency for right coronary artery: ITA, 11 of 14 grafts (79%); vein grafts, 286 of 464 (62%); and circumflex: ITA, 44 of 51 grafts (86%); vein grafts, 305 of 493 (62%).

Ten-year survival curves for the entire series and specific subsets are shown in Figure 1. Ten-year actuarial survival was 69.3% for those discharged alive after reoperation. The patients operated on in the initial experience, 1967 to 1978, enjoyed a significantly higher 10-year survival compared with patients in the next three cohorts. However a comparison of clinical, angiographic, and operative characteristics among the cohorts indicates that the 1967 to 1978 series was composed of lower-risk patients with respect to age, extent of coronary atherosclerosis, and left ventricular function. Patients who were operated on be-

cause of graft failure and progression of native vessel atherosclerosis had significantly lower 10-year survival rates, as did patients older than 65 years compared with younger patients. Patients with severe angina, any major comorbidity, severe left main coronary artery narrowing, moderate-to-poor left ventricular performance, and those who did not have an internal thoracic artery graft at either operation had significantly lower 10-year actuarial survival compared with their counterparts. The 10-year survival rate for women was 62.7%; for men it was 69.3% (NS).

Descriptors of late outcome varied from cohort to cohort, but left main coronary artery narrowing of 50% or more and left ventricular dysfunction consistently affected late survival throughout the entire experience. Significant variables are listed by cohort in the Appendix.



† 1979-81, 1982-84, 1985-87 curves are superimposed
* Diabetes, Hypertension, Peripheral Vascular Disease or Cigarette Smoking
+ Internal Thoracic Artery (ITA) graft used at either first or second operation

FIGS. 1A-I. (A) Ten-year actuarial survival and event-free survival rates for 2429 hospital survivors were 69.3% and 41.2%, respectively. (B) The earliest group, 1967-1978, enjoyed a significantly higher 10-year survival rate, 74.5%, than the first three cohorts, whose curves are virtually superimposed and reach 67.4% at 10 years. (C) Analysis of longevity by angiographic indication group shows that patients reoperated on for graft failure or progressive atherosclerosis had a better ($p = 0.0018$) 10-year survival rate than patients who experienced both progression and graft failure, 75.5% and 70.4% versus 63.4%, respectively. (D) Patients younger than 65 years before reoperation had a significantly better 10-year survival rate, 72.0%, than their older counterparts, 50.8% ($p = 0.0001$). (E) Survival rate by NYHA angina functional class shows I-II achieved 69.1% and III-IV 63.5% ($p < 0.0001$). (F) Comorbidity was defined as diabetes, hypertension, peripheral vascular disease, and cigarette smoking. Those with no comorbidity had a 10-year survival rate (77.1%) significantly greater than those with one or all comorbid conditions (63.7%) ($p = 0.0001$). (G) The presence or absence of left main coronary artery narrowing $\geq 50\%$ significantly influenced 10-year survival rate, 71.9% versus 55.2% ($p = 0.001$). (H) Left ventricular performance before reoperation, stratified subjectively, demonstrated a wide range of 10-year survival rates: normal function 77.4%, mild impairment 70.3%, moderate dysfunction 56.4%, and severe impairment 45.1%. The survival difference between normal and poor performance is significant ($p = 0.0001$). (I) The performance of an internal thoracic artery graft either at the first or second operation affected long-term survival rate (72.6%) compared with vein grafts at both operations (65.5%) ($p = 0.004$).

Discussion

Among the first 1000 consecutive patients who had myocardial revascularization each year from 1971 to 1978, 3% had been reoperated on at our institution or elsewhere within 5 years of the first procedure. At 10 years 12% had undergone reoperation and by the 12th postoperative year, 17% had undergone reoperation.⁶ This estimated incidence of reoperation at year 15 rises to 30% (95% confidence interval, 29% to 32%).

Many factors intervene after operation, and not all fit statistical analysis. Progression of atherosclerosis is unpredictable and depends on heredity and serum lipid concentrations. The rate of reoperation is also influenced by age, left ventricular function, and comorbidity. The choice of conduits used in the first operation modifies the rate of reoperation significantly. The higher patency and relative freedom from graft atherosclerosis found in the patients who underwent internal thoracic artery bypass significantly reduces the reoperation rate.^{7,8} Previously we surveyed the first 1000 isolated primary coronary bypass patients operated on annually from 1971 to 1978. Of the measurable clinical, angiographic, and operative variables, use of vein grafts was the single greatest determinant of reoperation. Percutaneous transluminal coronary angioplasty doubtless spares some patients from reoperation, but quantitatively this protection and its effect are not yet known.

Our observational data in this report indicate that vein graft atherosclerosis is the leading cause of reoperation, more than progressive coronary atherosclerosis *per se*. Late graft closure, particularly after the fifth postoperative year, relates to vein graft atherosclerosis. This statement relies on demonstration of lesions in the conduit by angiography or a visual impression at surgery. Old conduits were removed infrequently for examination, but angiographic and microscopic observations correlate consistently.

The interval before reoperation continues to lengthen and, for patients in our 1985 to 1987 cohort, the mean duration before reoperation was approximately 9 years. As the frequency of left internal thoracic artery grafts to the anterior descending coronary artery increase and expanded use of thoracic arterial conduits gains favor, reoperation rates may decline and intervals between operations may lengthen further. Other factors that may decrease these rates include less traumatic vein preparation,^{9,10} use of antiplatelet agents,^{11,12} cessation of cigarette smoking,¹³ and reduction of serum lipids.^{14,15}

Trends in Patient Characteristics

A slightly reduced prevalence of severe angina before reoperation in the most recent cohort (1985 to 1987) compared with the earliest cohort (1967 to 1978) is probably due to improved antianginal therapy and possibly to

liberalization of selection criteria. Comorbidity in the form of diabetes, hypertension, obesity, and peripheral vascular disease rose in the reoperation candidates during the interval surveyed, which reflects patient age and lengthening interval between operations. Women did not become more frequent reoperation candidates over time.

Nearly all patients had multivessel disease, but left main narrowing of 50% or more was seen significantly more often (25%) in reoperation than in primary surgical candidates (average, 10% to 12%). Twenty-five to thirty per cent of reoperation patients lost previously normal left ventricular function in the interval between operations.

We reported previously that vein graft failure was the most frequent angiographic reason for reoperation. In most cases late vein graft failure relates to atherosclerosis in the vein conduit. Internal thoracic artery graft atherosclerosis necessitating reoperations is rare.

Evolution of Technique

Changes in technique in 20 years involve (1) techniques of reentry, (2) myocardial protection, and (3) blood conservation. The gas-powered oscillating saw has replaced older re-entry techniques. Myocardial protection has changed from normothermic arrest to core cooling with cold potassium cardioplegia. Cardioplegic solutions were used in all patients in the last cohort, compared with 16%, 80%, and 97% in the first, second, and third cohorts, respectively. Beginning in 1988 this technique of crystalloid cardioplegia was supplanted by blood cardioplegia and, in early 1989, we began an antegrade and retrograde (coronary sinus) delivery protocol¹⁶ for most reoperation candidates. Blood conservation in the form of a regionally heparinized blood processing system, retrieval of all oxygenator blood, and transfusion of shed blood after operation^{17,18} have significantly reduced transfusion requirements. Because 20% of blood transfusions may result in some adverse effect,¹⁹ we infer that some morbidity has been avoided.

These three advances in technique allow greater time for exposure and complete revascularization. Retrograde cardioplegia cools the subendocardium more than does antegrade cardioplegia delivery and is especially suited for left ventricular regions involved with a totally obstructed coronary artery.²⁰ Rather than dissection of the beating heart, mobilization of the adhered left ventricle is facilitated by administration of cardioplegia first. Previous patent internal thoracic artery grafts must be identified and temporarily occluded. A patent atherosclerotic vein graft is best managed by a no-touch technique followed by early division near the distal anastomosis. A new graft is then attached to that artery first so that regional cooling is preserved. The trend toward arterial grafting is shown by new internal thoracic artery graft

usage, which rose from 27% in the 1967 to 1978 period to 67% of cases in the 1985 to 1987 period.

Results in the 1985 to 1987 Cohort

Patients in this latest cohort had significantly fewer perioperative new Q-wave infarctions. This finding is attributed to routine use of cardioplegia solutions and early defunctionalization of patent, atherosclerotic vein grafts. The reduction in transmural myocardial infarction rates occurred in a significantly older patient group who had more diabetes, hypertension, peripheral vascular disease, three-vessel disease, left main lesions, vein graft atherosclerosis, and worse left ventricular performance compared with the first three cohorts. After the initial experience from 1967 to 1978, mortality and other morbidity rates generally declined in this reoperation experience, but these rates were significantly higher than complications related to the first surgery.

10-year Survival

Actuarial 10-year survival for each cohort and the composite series, *i.e.*, all 2509 patients, reveals the following. (1) Patients reoperated on in the initial experience, 1967 to 1978, showed significantly higher survival and event-free survival rates. Higher survival in this initial cohort occurred because of their significantly younger age, less extensive coronary artery disease, and better left ventricular performance before reoperation. (2) We found a significant adverse effect on longevity in patients 65 years or older compared with younger patients, severe angina before reoperation, left main disease of 50% or more compared with lesser or no left main lesion, severe left ventricular dysfunction, reoperation for both graft closure and progressive atherosclerosis, saphenous vein grafts only at both operations, any or all of the major forms of comorbidity (diabetes, hypertension, peripheral vascular disease, and current cigarette smoking). Of the conditions constituting comorbidity, peripheral vascular disease alone showed the greatest adverse influence on 10-year survival. We found no significant difference in long-term survival whether the patient was operated on for graft closure or for progressive atherosclerosis, and gender differences had no effect. As descriptors of late outcome, left main narrowing of 50% or more and left ventricular dysfunction worsened the prognosis more consistently than other variables for individual cohorts.

Functional Status

Angina relief is acknowledged to be less after reoperation compared with the first operation.^{4,21} We presume that diffuse coronary atherosclerosis and left ventricular impairment underlies this consistent finding. Noteworthy

in this report is the finding that patients with no angina or mild angina before reoperation tended to remain in NYHA functional class I or II (mean follow-up, 72 months), whereas those in classes III and IV before operation may achieve a long-term asymptomatic status but are more likely to have recurring severe angina compared with patients who had mild angina or no symptoms before reoperation.

Postreoperative angiography was reserved almost exclusively for patients with recurring symptoms. We found vein graft patency of 65% and internal thoracic artery patency of 88% after a mean of 58 months; these rates are lower than those found 5 years after the first operation.

Coronary artery reoperations are undertaken for angina or ischemia related mainly to three-vessel or left main coronary artery disease. The interval between operations has lengthened throughout this experience and now approaches 9 years. Vein graft atherosclerosis has become the major angiographic indication for reoperation.

A comparison of the 1985 to 1987 patients with earlier cohorts reveals a higher-risk population of candidates for reoperation. Advancing age, increased comorbidity, more three-vessel and left main coronary artery disease, and greater left ventricular dysfunction are documented in the most recent group. Improved myocardial protection permits wider use of the internal thoracic artery, more grafts per patient, and consequently more complete revascularization.

Operative risk is related to age and left main coronary artery disease more than any other factors. Hospital mortality rate has consistently been less than 5%. Myocardial protection accounts for a significant reduction in new Q-wave perioperative myocardial infarction, which constitutes the single greatest improvement in recent history of isolated coronary artery operations. Further advances in myocardial protection will provide the key to greater safety in these increasingly frequent procedures.

Survival is influenced by patient age, medical status, and angiographic findings before reoperation. Those who received an internal thoracic artery graft to the anterior descending artery, either at the first or the second operation, fared significantly better than those with vein grafts only.

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Appendix

TABLE 5. *Variables Tested for Operative and Late Risk*

1. Age (years): <65, ≥65
2. Sex
3. Interval between operations: months <60, ≥60
4. Internal thoracic artery graft at first operation (no, yes)
5. Internal thoracic artery graft at second operation (no, yes)
6. Angiographic reason for reoperation (progressive atherosclerosis, graft failure, combination of progressive atherosclerosis and graft failure)
7. Obesity (no, yes)
8. Hypertension (no, yes)
9. Diabetes (no, yes)
10. Peripheral vascular disease (no, yes)
11. Cigarette smoking (no, yes)
12. Preoperative angina NYHA functional class (I, II, III, IV)
13. Congestive heart failure (no, yes)
14. Extent of disease: (one, two, three, left main)
1/2 versus 3/left main
15. Left ventricular function (normal/mild, moderate/severe)
16. Referral (internal, external)
17. Units of blood: units (0, >0)
18. Cohort (1967-1978, 1979-1981, 1982-1984, 1985-1987)
19. Total number of grafts per patient at reoperation
20. Total number of grafts per patient at first operation
21. Completeness of revascularization at reoperation
22. Preoperative cholesterol value
23. Preoperative triglycerides value

TABLE 6. 95% Confidence Intervals for the Relative Risk Estimates: Multivariate Model of Operative Risk by Cohort and Overall

Risk Factors	1967-1978 20/433	1979-1981 10/439	1982-1984 21/623	1985-1987 29/1009	1967-1987 80/2509	Relative Risk	95% Confidence Interval
Left ventricular dysfunction	0.02			0.05	0.02	1.7	1.1-2.8
Age (decade)		0.03	0.02	0.002	0.0009	1.7	1.2-2.3
Current cigarette smoking				0.01	0.01	1.9	1.1-3.1
Left main narrowing ≥ 50%	0.002		0.0001		0.0001	6.9	2.6-18.3
Three-vessel disease					0.05	2.6	1.007-6.7
Blood transfused (units)					0.02	2.1	1.1-3.8
Angina NYHA class III/IV					0.02	2.1	1.1-3.7
Interval in months > 60	0.004				0.02	2.1	1.1-4.0
No ITA at first operation					0.04	2.3	1.03-5.2
Cohort 1967-1978					0.002	2.7	1.5-5.0

NYHA, New York Heart Association.

ITA, internal thoracic artery.

TABLE 7. 95% Confidence Intervals for the Relative Risk Estimates: Multivariate Model of Long-term Survival

Risk Factors	1967-1978	1979-1981	1982-1984	1985-1987	1967-1987	Relative Risk	95% Confidence Interval
Left ventricular dysfunction	0.01	0.0001	0.0001	0.0001	0.0001	1.9	1.6-2.3
Age	0.0001	0.002	0.003	0.001	0.0001	1.04	1.03-1.05
Diabetes		0.0001			0.0001	1.6	1.3-1.9
Current cigarette smoking	0.02	0.0006			0.0001	1.5	1.3-1.9
Hypertension	0.0001	0.01			0.0002	1.4	1.2-1.7
Left main narrowing ≥ 50%		0.001			0.0001	2.0	1.5-2.7
Three-vessel disease		0.02			0.0001	1.6	1.3-2.1
New Q-wave myocardial infarction	0.007	0.0001			0.002	1.6	1.2-2.3
Angina NYHA class III/IV			0.0009		0.003	1.4	1.1-1.7
Peripheral vascular disease		0.01			0.001	1.5	1.2-2.0
Interval in months > 60		0.02			0.006	1.003	1.001-1.005
No ITA at first operation	0.005			0.002	0.03	1.5	1.09-1.9

NYHA, New York Heart Association.

ITA, internal thoracic artery.

TABLE 8. Primary Versus Reoperation Mortality and Morbidity

Mortality and Morbidity	Primary* (n = 16,996)		Reoperation (n = 2509)		p value
	(n)	(%)	(n)	(%)	
Operative mortality	240	1.1	80	3.2	<0.0001
Perioperative myocardial infarction	415	2.1	148	5.9	<0.0001
Bleeding	891	4.8	155	6.2	<0.0001
Respiratory insufficiency	377	2.0	98	3.9	<0.0001
Neurologic deficit	294	1.6	46	1.8	NS
Wound complication	302	1.6	41	1.6	NS

* First 1000 cases annually from 1971 to 1987.

DISCUSSION

DR. O. WAYNE ISOM (New York, New York): The contributions by the Cleveland Clinic in the surgical treatment of coronary disease over the past quarter of a century have certainly been monumental and the reports over the years have been enlightening to all of us. I appreciate the opportunity to review the manuscript in detail before the meeting.

I have five questions combined with a few comments. The first is: Was there a reason that the cohorts were divided up into an 11-year

period between 1967 and 1978 and a 3-year period between 1979 and 1981, and 2-year periods between 1982 and 1984 and between 1985 and 1987? Was there some specific change in technique in these particular periods, or was there a change in composition of the surgeons during that period, or perhaps was this just an arbitrary decision to divide them up into equal numbers even though the last group is higher?

The second question is that in all groups operated on between 1967 and 1987, the mean age at first operation ranged between 49 and 52. The mean age in the second operation, in the last two groups was between 58 and 60.

In the past 5 years at New York Hospital Cornell Medical Center, the mean age in a little over 4000 patients undergoing coronary bypass surgery for the first time has been 64 years of age, and for the second operation the mean age has been slightly more than 70 years. I wonder if you have noticed the difference in your ages coming to first and second operation in the last 2 years. I know from conversations with many of my colleagues across the country that they, too, have noticed an increase in age and severity in their own series.

The operative mortality of less than 3% in this last group and the low incidence of a perioperative myocardial infarction is certainly admirable.

Because ongoing myocardial ischemia in the emergency patient undergoing surgery certainly is associated with a higher operative mortality and a higher perioperative infarction rate, how many of your patients were having ongoing myocardial ischemia requiring an intra-aortic balloon or IV nitroglycerin? Also how many were transferred to the Cleveland Clinic as an emergency in an unstable condition?

You mention in the manuscript that one of the reasons for the improvement is better myocardial preservation. Would you expand on your reasons for changing from crystalloid to blood cardioplegia during this period and also what prompted you to use retrograde coronary sinus cardioplegia recently?

A fourth question: in your earlier report of the first 1500 operations reported in 1987, you had Kaplan-Meier survival curves and event free curves at 10 years, which is also presented in this paper. In the first cohort dating back 20 years, were you able to carry out 15- and 20-year survival curves in this group, or did you not have sufficient numbers to construct these curves at 15 and 20 years?

And finally, a hypothetical question. Because a 10-year patency rate of a saphenous vein graft in your series is somewhere around 50%, when do you reoperate on a patient, for example, at 5 years with two widely patent vein grafts angiographically, which also at surgery appear to be soft and free of disease with two other closed grafts, at what time after operation would you electively replace all of those grafts?

DR. FLOYD D. LOOP (Closing discussion): In order of queries, the cohort sizes were entirely arbitrary. After the advent of crystalloid car-

dioplegia for myocardial protection, no major technical changes occurred during the 1970s. We, too, noticed that patients were considerably younger in our reoperation series. Our mean age for primary coronary bypass patients reached 63 years in 1989, but has been consistently younger through all cohorts of patients who have undergone reoperation. This younger age signifies a predilection for coronary atherosclerosis, and possibly for progressive atherosclerosis in both native vessels and vein grafts. Only a small minority of reoperation patients had acute ischemia that required preoperative intra-aortic balloon support. Whereas emergency surgery is seen with increasing frequency among primary coronary bypass patients, this was not the case in our reoperation series.

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If vein grafts have been in place longer than 7 years, or if they show angiographic evidence of atherosclerosis, we favor replacement of the vein graft, provided that the risk is not enhanced by the lengthened procedure.

In closing, we emphasize that reoperative coronary artery surgery requires a plan at the outset. Technical considerations in reoperation include re-entry, exposure, myocardial protection, prevention of vein graft atheroembolism, and the management of patient internal thoracic artery grafts. For the most part these technical problems have been solved, and increasing safety of coronary bypass reoperations has been documented by this report.

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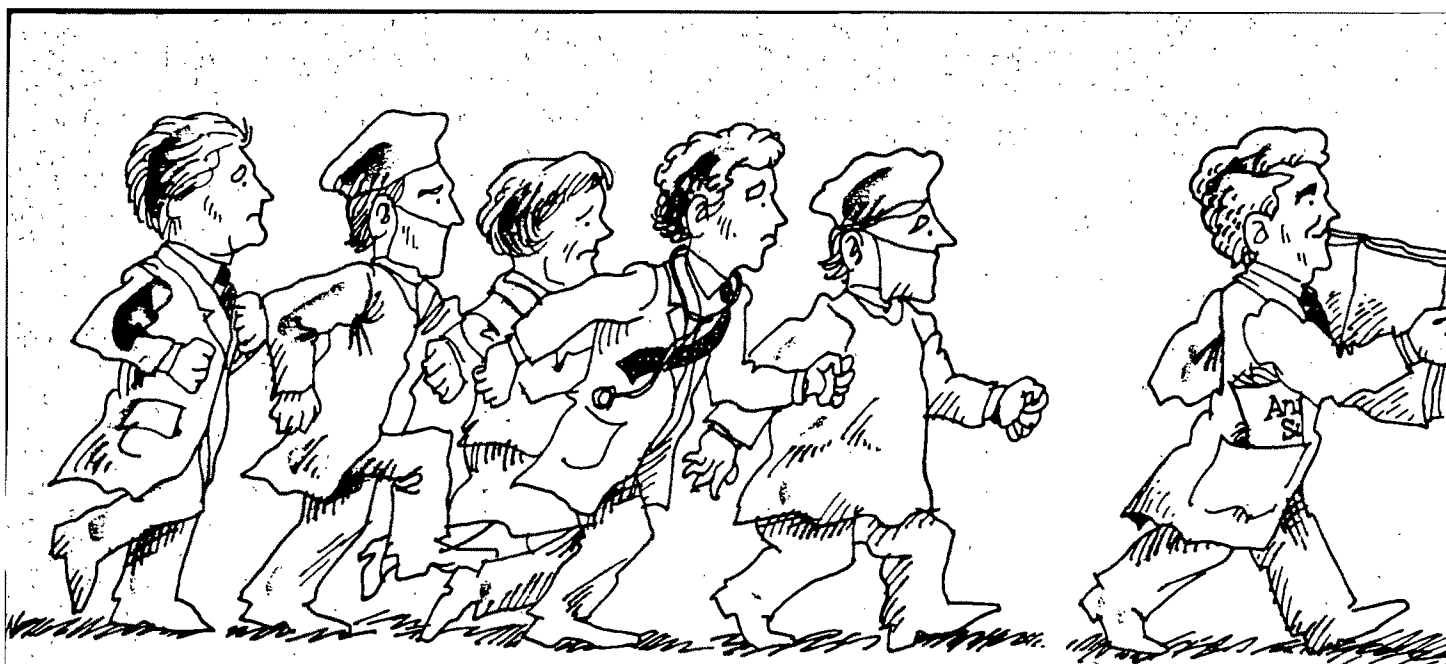
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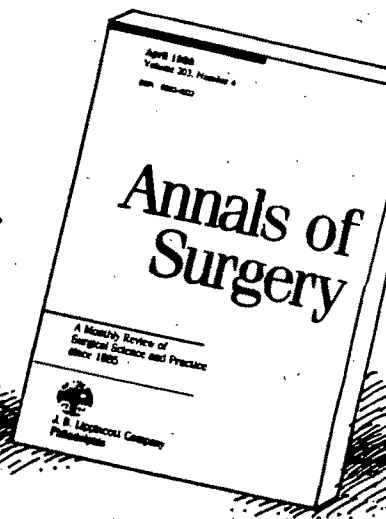
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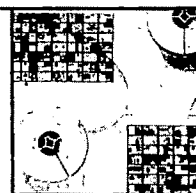
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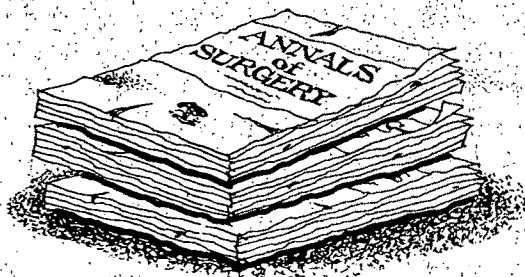
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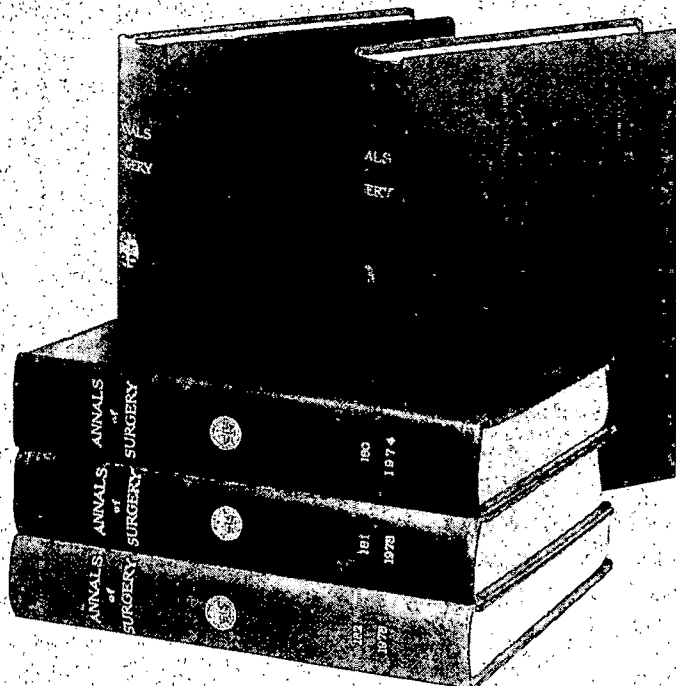
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